IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ABBOTT LABORATORIES and ABBOTT RESPIRATORY LLC Plaintiffs, v. TEVA PHARMACEUTICAL INDUSTRIES, LTD. and TEVA PHARMACEUTICALS USA, INC., Defendants.	C.A. No. 10-57 (SLR)(MPT) CONSOLIDATED **REDACTED PUBLIC VERSION FILED 1/13/12**
ABBOTT LABORATORIES and ABBOTT RESPIRATORY LLC Plaintiffs, v. WATSON LABORATORIES, INC. - FLORIDA, Defendant.	

JOINT APPENDIX OF INTRINSIC AND EXTRINSIC EVIDENCE

VOLUME VI
(JA004361-JA005113)

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DECLARATION OF FRANK SACKS IN SUPPORT OF PLAINTIFFS' OPENING CLAIM CONSTRUCTION BRIEF

I, Frank Sacks M.D., submit this declaration in support of the Opening Claim Construction Brief of Plaintiffs Abbott Laboratories and Abbott Respiratory LLC (collectively, "Abbott").

I. INTRODUCTION

1. I have been retained by Abbott to provide expert opinions and testimony in the above-captioned case. I understand that Abbott has filed suit against Teva Pharmaceuticals

USA, Inc. and Teva Pharmaceutical Industries, Ltd. (collectively, "Teva") and Watson Laboratories, Inc.-Florida ("Watson") (collectively "Defendants") and has alleged that Defendants' filing of certain Abbreviated New Drug Applications ("ANDAs") for the approval of generic versions of Abbott's drug SIMCOR® infringes certain identified claims of U.S. Patent Nos. 6,080,428 ("the '428 patent"), 6,129,930 ("the '930 patent"), 7,011,848 ("the '848 patent"), 6,818,229 ("the '229 patent"), 6,406,715 ("the '715 patent"), 6,676,967 ("the '967 patent"), and 6,746,691 ("the '691 patent") (collectively, the "Patents-in-Suit"). I have been asked to provide some background regarding hyperlipidemia and the treatment of hyperlipidemia, and, in particular, the use of niacin to treat hyperlipidemia in the early to mid-1990s. In addition, I have been asked to comment on the meaning of certain terms in the claims of the Patents-in-Suit from the perspective of one of ordinary skill in the art in the early to mid-1990s.

A. Background

2. I am a Professor of Cardiovascular Disease Prevention at the Harvard School of Public Health, a Professor of Medicine at Harvard Medical School, and a Senior Physician at the Channing Laboratory and Cardiology Division of Brigham & Women's Hospital. My responsibilities include teaching, practicing at the Hyperlipidemic Clinic in the Cardiovascular Division at Brigham and Women's Hospital from 1984 to 2010, and participating as a member, chair or fellow in numerous professional societies, committees and editorial boards.

3. I am a fully licensed physician in the State of Massachusetts.

4. My professional interests include research and public policy in nutrition, cholesterol disorders, hypertension, and cardiovascular disease. I have 179 peer-reviewed publications of original research, plus over 70 reviews, editorials and chapters relating to these

interests. In addition, I am the editor or co-editor of three books relating to cardiovascular disease, cholesterol disorders, and nutrition.

5. In 1970, I received a Bachelor of Science degree in Biology with an emphasis on biochemistry from Brown University. In 1977, I received the Doctor of Medicine degree from Columbia University College of Physicians and Surgeons. From 1977 to 1978, I was a Resident in Surgery at University Hospital in Madison, Wisconsin. From 1977 to 1993, I held appointments at various hospitals and institutions, including Harvard Medical School, Brigham and Women's Hospital, Children's Hospital, and Beth Israel Hospital, all in Boston.

6. I have specialized in treating patients suffering from hyperlipidemia since 1982, when I began a two-year training (1982-84) in the Lipid Clinic, Children's Hospital, with a renowned lipidologist, Jan Breslow. This training was part of a fellowship grant called a Clinician-Scientist Award from the American Heart Association, which was designed to bridge the transition from fellowship training to first faculty position. In 1984, I returned to Brigham & Women's Hospital and was appointed Associate Physician, and Assistant Professor of Medicine at Harvard Medical School.

7. In 1984, I was given an attending physician appointment at Brigham & Women's Hospital in the newly formed Vascular Medicine Division to serve as the hospital's expert in hyperlipidemia as a cause of heart disease. I practiced in this clinic, which is now part of the Cardiology Division, until September, 2010.

8. From 1993 to 2000, I was an Associate Professor in the Department of Nutrition at the Harvard School of Public Health; in 2000, I became a full tenured professor at Harvard University at the Harvard School of Public Health.

9. In addition to my appointment at the Harvard School of Public Health, I have a second professional appointment as full professor at Harvard Medical School. I became a full professor of medicine in 2004 following my position as an Associate Professor of Medicine, from 1992 to 2004, and Assistant Professor of Medicine from 1984 to 1992. In these capacities, I conducted research in lipid disorders, trained medical students and residents in internal medicine and primary care, and trained fellows subspecializing in cardiology or endocrinology in the diagnosis and treatment of lipid disorders, as well as continued to treat patients in the area of lipid disorders in the Cardiology Clinic.

10. Finally, since 2004, I have served as a Senior Physician at Brigham & Women's Hospital, conducting research in hyperlipidemia, teaching as mentioned above, and treating patients for dyslipidemia, hyperlipidemia, and cholesterol disorders. My clinical activities are in the Cardiology Division, and my research activities are in the Channing Laboratory, a research division at Brigham & Women's Hospital. In particular, as a practicing physician, I have treated patients suffering from dyslipidemia with various formulations of extended and immediate release niacin from 1984 through September, 2010.

11. In addition to treating patients suffering from lipid disorders, in connection with my teaching responsibilities, I regularly lecture on hyperlipidemia treatment in particular to medical students and practitioners at Harvard Medical School, the Harvard School of Public Health and Brigham and Women's Hospital.

12. I am teaching or have taught the following classes at the Harvard School of Public Health:

Nutritional Epidemiology (1986-1998);

Nutritional Aspects of Human Disease (1986-1992);

Cardiovascular Disease Epidemiology (1988-2011);

The Science of Human Nutrition; Nutritional Biochemistry (Course Director, 1998-2009); and

Scientific Writing (Course Director, 2004-2011).

13. I am teaching, or have taught the following classes at Harvard Medical School:

Principles of Pharmacology. Lecturer on hyperlipidemia treatment (1990-2006, Full First-year MD and PhD classes);

Clinical Epidemiology. Lecturer on cardiovascular disease epidemiology and clinical trials (2000-2005, Full first-year MD class);

Preventive Medicine and Nutrition (2000-2003, Full second-year MD class); and

Cardiovascular Division Clinic: clinical teaching of HMS students and house staff in hyperlipidemia (1984-2010).

14. I have been teaching Continuing Medical Education classes at Harvard Medical School on the management of hyperlipidemia since 1986.

15. I have acted as a guest lecturer or panelist at over 70 regional, national or international symposiums and seminars since 1999 alone, most of which focused on the diagnosis and treatment of lipid disorders.

16. I have also served as Principal Investigator in numerous clinical trials relating to heart disease and hyperlipidemia, including:

2008-10 Effect on apolipoprotein C-III, of mipomersen, a novel antisense oligonucleotide drug that suppresses the production in the liver of apolipoprotein B and its associated lipoproteins, VLDL and LDL, in hypercholesterolemia. Apolipoprotein C-III has a detrimental effect on VLDL and LDL metabolism, and the results showed that the drug suppresses it. (Grant from ISIS Pharmaceuticals to Harvard University: F. Sacks, Principal Investigator);

2009-10 Establishing a platform for evaluating the effects of diet and drugs on the function of human HDL. (Harvard Catalyst Grant for innovative research with translational potential: F. Sacks, Principal Investigator);

2010-15 Diet and human HDL metabolism. A grant from National Heart. Lung and Blood Institute to determine how dietary fat and

carbohydrate affect the principal function of HDL in removing cholesterol from the body (F. Sacks, Principal Investigator);

1996-2002 Dietary Approaches to Stop Hypertension ("DASH") and Sodium Trial - a multicenter trial on blood pressure and lipids of dietary patterns and sodium reduction (Grant from National Heart, Lung, and Blood Institute: F. Sacks Principal Investigator);

2003-07 VLDL and LDL particle types as CHD risk factors (NIH: R01 HL070159) (Grant from National Heart, Lung, and Blood Institute: F. Sacks Principal Investigator);

2002-06 Apo A2, Cl and C2 and diet in human apoB metabolism (NIH: 1R01 HL69376) (Grant from National Heart, Lung, and Blood Institute: F. Sacks, Principal Investigator);

1997-2002 "Kinetics of human postprandial lipoprotein metabolism" (NIH RO1HL56210) (Grant from National Heart, Lung, and Blood Institute: F. Sacks, Principal Investigator);

1997-2001 "Lipoprotein ancillary project in the CARE trial," study of lipoprotein subtractions to predict cardiovascular events, and differential response to treatment (Grant from Bristol-Myers Squibb to Brigham & Women's Hospital: F. Sacks, Principal Investigator);

1988-96 "Cholesterol and Recurrent Events (CARE) trial": a study in 4,159 patients in 80 centers in the US and Canada that proved that cholesterol lowering by a statin, pravastatin, in patients who had average cholesterol levels prevented heart attacks and strokes. (Grant from Bristol-Myers Squibb to Brigham & Women's Hospital: F. Sacks, Principal Investigator); and

1986-97 "Postmenopausal estrogens and atherosclerosis"; study of effect of sex hormones on lipoprotein metabolism (NIH: RO1 HL34980) (Grant from National Heart, Lung, and Blood Institute: F. Sacks, Principal Investigator).

In addition, I served as co-investigator on many other grants from NIH and other organizations.

17. I have also conducted or participated in clinical trials regarding niacin treatment, including time-release, sustained release, and immediate release formulations of niacin. The results of several of these studies have been published as follows:

Helen L. Figge, *et al*., "Comparison of Excretion of Nicotinuric Acid After Ingestion of Two Controlled Release Nicotinic Acid Preparations in Man," J CLIN PHARMACOL 1988; 28:1136-1140;

James D. Alderman, *et al*., "Effect of Modified, Well Tolerated Niacin Regimen on Serum Total Cholesterol, High Density Lipoprotein Cholesterol, and the Cholesterol to High Density Lipoprotein Ratio," AM J CARDIO. 1989; 64:725-729;

Frank M. Sacks, *et al*. for the Harvard Atherosclerosis Reversibility Project (HARP) Group, "The Effect on Coronary Atherosclerosis of Decrease in Plasma Cholesterol Concentrations in Normocholesterolemic Patients," LANCET 1994; 344:1182-86; and

Richard Pasternak, *et al.*, "Effect of Combination Therapy with Lipid-Reducing Drugs in Patients with Coronary Heart Disease and 'Normal' Cholesterol Levels," ANN. INTERN. MED. 1996; 125:529-540.

18. During my career, I have been a member, chair or speaker with numerous professional committees. Some of my major committee assignments include:

2000-2011	Organizing Committee and Co-Chair, Lipoprotein Kinetics Conference, Satellite Meeting to the Arteriosclerosis, Thrombosis and Vascular Biology Council Meeting, American Heart Association
2001	National Cholesterol Education Program, Adult Treatment Panel III, Reviewer of Year 2002 guidelines
2006	NIH, NHLBI: Consultant group on clinical trial design for lipid drugs
2000-	American Heart Association, Nutrition Committee, Member, Vice-Chair, Chair 2010-12
2008-2011	American Heart Association, Leadership Committee, Council on Nutrition Physical Activity and Metabolism
2008-2011	NHLBI Clinical Guidelines for Cardiovascular Risk Reduction, National Cholesterol Education Program Adult Treatment Panel IV ("ATP IV") Expert Panel member
2008-	NHLBI Clinical Guidelines for Cardiovascular Risk Reduction, Lifestyle Working Group member
2009	Institute of Medicine, National Academy of Sciences, consultant on treatments for hypertension
2010-	Endocrine Society, Guidelines Panel on Treatment of High Triglycerides
2010-	National Kidney Foundation, KDIGO (Kidney Disease Improving Global Outcomes) Guidelines Committee for Treatment of Dyslipidemia

19. I am a fellow in several professional societies relating to my field. Since 1983, I have been a fellow with the Council on Arteriosclerosis for the American Heart Association. Since 1983, I have also been a fellow with the Council on Epidemiology for the American Heart Association. Since 1994, I have been a fellow with the American Society of Clinical Nutrition. Since 2000, I have been a fellow with the Council on Nutrition, Metabolism, and Physical Activity for the American Heart Association.

20. I am a member of the editorial boards of the Journal of Lipid Research; and Associate Editor of the Journal of Clinical Lipidology. I was Associate Editor of the American Journal of Clinical Nutrition from 2007-2010.

21. I have acted as a guest lecturer or panelist at over 60 regional, national, or international symposiums and seminars since 2004 alone, most of which focused on the diagnosis and treatment of lipid disorders.

22. During my career, I have received honors and awards, including:

1974	Annual Prize for Predoctoral Research, Society for Epidemiologic Research
1980-1982	Individual Postdoctoral Research Award, United States Public Health Service
1982-87	Clinician Scientist Award, American Heart Association
1986	Travenol Award Lecture, American College of Nutrition
1987-1992	Established Investigator Award, American Heart Association, Eugene Braunwald, Sponsor
1999	Pierre Bois Lecturer, McGill University and the University of Montreal
2002	Myant Lecturer, British Hyperlipidemia Society
2011	American Heart Association 2011 Research Achievement Award for lifetime research accomplishments

23. My complete *curriculum vitae* is attached as Exhibit A.

II. BACKGROUND OF THE INVENTION

A. Hyperlipidemia

24. Hyperlipidemia (or dyslipidemia as it is sometimes also called) refers to the presence of raised or abnormal levels of lipids and/or lipoproteins in the blood. Although it is most often associated with elevated low density lipoprotein cholesterol ("LDL cholesterol"), hyperlipidemia can also describe elevated total cholesterol ("TC") or triglycerides ("TG"), or lipoprotein(a) ("Lp(a)"); or abnormally low levels of high density lipoprotein cholesterol ("HDL cholesterol").

25. We often characterize cholesterol as "bad cholesterol," "good cholesterol," and "total cholesterol." "Bad cholesterol" includes cholesterol contained in low density lipoproteins ("LDL"); in very low density lipoproteins that are measured commonly by the blood triglycerides concentration; and lipoprotein(a) ("Lp(a)"). "Good cholesterol" refers to the cholesterol contained in high density lipoproteins ("HDL"). "Total cholesterol" is measured directly in blood and is the sum of cholesterol in VLDL, LDL, Lp(a), and HDL.

26. Hyperlipidemia is associated with an increased risk of atherosclerosis, characterized by excessive cholesterol accumulation forming plaque in the arterial walls; and inflammation in the arterial walls; blocking the flow of blood in the heart, brain and other organs and causing heart attacks and strokes.

27. Atherosclerosis is the leading cause of heart attacks, strokes, and peripheral vascular disease. For example, in the United States alone, 13 million adults have been diagnosed with coronary heart disease, a condition that can often lead to heart attacks, 8 million people have been diagnosed with peripheral arterial disease, and approximately 4.8 million people in the United States have had a stroke.

28. Treatment of atherosclerosis may require invasive, dangerous and expensive procedures. For example, each year, there are over 1 million angioplasties (operations to unblock a coronary artery) and over 500,000 coronary bypass surgeries (open-heart surgeries to bypass the blocked section of the coronary artery).

B. Niacin and the Treatment of Hyperlipidemia

29. Niacin has been used for fifty years to treat both blood cholesterol disorders and triglyceride disorders.

30. In effective doses, niacin decreases the amount of "bad cholesterol" in the bloodstream. Niacin blocks the breakdown of fats in the body's adipose (fatty) tissue, decreasing the amount of fatty acids in the bloodstream. With less free fatty acids in the bloodstream, the liver secretes less bad cholesterol.

31. In effective doses, niacin also increases HDL cholesterol by increasing the liver's synthesis of HDL and by reducing the rate of removal of HDL from the blood.

32. The first niacin formulations to be used for the treatment of cholesterol disorders were "immediate release" formulations – *i.e.*, products formulated without the intent to modify the rate of release of the drug after ingestion.

33. When provided at therapeutic daily doses, immediate release niacin was effective in lowering total cholesterol, LDL cholesterol, triglycerides and Lp(a), and increasing HDL cholesterol.

34. Immediate release formulations, typically administered several times per day, are commonly associated with "flushing" – redness, warmth, tingling and/or itching of the skin.

35. In my experience prescribing immediate release niacin to hyperlipidemic patients and observing their responses to it, the vast majority of patients experience flushing.

The degree of flushing experienced varies from mild to severe. The typical niacin flush is extremely uncomfortable and disturbing, and it may take several weeks or months for a patient to develop a tolerance to a dose of immediate release niacin that is enough to be therapeutic for dyslipidemia. In some cases, patients experiencing flushing – especially for the first time – may panic and sometimes end up in the emergency room.

36. As a result of the prevalence of flushing with immediate release niacin at therapeutically effective doses, many doctors are reluctant to prescribe immediate release niacin and many patients are unwilling to take it or discontinue treatment, notwithstanding its effectiveness in treating hyperlipidemia.

37. "Sustained release" formulations of niacin were designed to avoid or reduce the flushing associated with immediate release niacin. Sustained release formulations slow the rate of absorption of niacin by the body and reduce the peak level of the drug in the blood.

38. However, clinical studies showed that early sustained release formulations were not as effective at lowering triglycerides or raising HDL as immediate release niacin.

39. Worse, clinical studies showed (and my personal experience prescribing sustained release niacin formulations confirmed) that sustained release formulations produced adverse side effects, including hepatotoxicity (liver damage), increased fasting glucose levels (dangerous for patients also suffering from diabetes), increased levels of uric acid (which can lead to gout), activation of stomach ulcer with hemorrhage, and body odor. As a result of this decreased efficacy and increased potential for serious side-effects, many clinicians, including me, avoided prescribing sustained release niacin to patients for treatment of hyperlipidemia, except in cases of severe hyperlipidemia or very high risk of heart attack and stroke where other treatments were not effective.

40. Because of the unique effectiveness of niacin at certain doses to increase HDL and lower triglycerides, and the unique effectiveness of statins to decrease LDL, it might have been desirable to combine the two therapies to achieve maximum potential to treat dyslipidemia. However, the combination of statin therapy with niacin increases the risk of developing the side effects typically associated with statin therapy, such as myopathy and rhabdomyolysis. In addition, because statin therapy is also associated with increases in liver enzymes, combination of niacin therapy with a statin increases the risk of developing the hepatotoxicity associated with sustained release niacin therapy.

41. At the time of the inventions of the Patents-in-Suit, there was a need for an alternative hyperlipidemia treatment – one that retained the benefits of niacin while avoiding the side effects associated with the existing immediate release and sustained release forms of niacin. By offering a means of achieving the lipid-altering effects of immediate release niacin as well as the reduced flushing obtainable with other formulations of sustained release niacin, but without the dangerous side effects associated with prior sustained release niacin formulations, the methods of treatment and compositions claimed by the Patents-in-Suit solved the problems experienced with prior immediate release and sustained release forms of niacin which limited their utility in the treatment of hyperlipidemia.

III. OPINION

A. Ordinary Skill in the Art

42. I understand that for the purposes of construing the disputed claim terms, it is necessary to examine those terms from the viewpoint of a person of ordinary skill in the art at the time of the invention.

43. The arts relevant to the Patents-in-Suit are the design, formulation, and testing of oral solid dosage forms; biopharmaceutics and pharmacokinetics; and the treatment of patients with lipid disorders.

44. In my opinion, a person of ordinary skill in the art with respect to the Patents-in-Suit in the early to mid-1990s would have basic knowledge of solid oral dosage formulation, biopharmaceutics and pharmacokinetics, and the treatment of lipid disorders, either through experience working in drug development and formulation or through training (such as a degree in pharmacy or a medical degree), and several years of experience or training in one or more of the relevant arts.

B. Disputed Claim Terms

45. I have been asked to provide my opinion regarding the understanding of a person of ordinary skill in the art in the early to mid-1990s regarding the following terms:

- "effective antihyperlipidemic amount" ('428 patent, claim 1; '930 patent, claims 18, 51, 115, 133; '848 patent, claim 1); "effective amount of an intermediate release nicotinic acid formulation" ('967 patent, claim 1, 16);
- "effective lipid-altering amount" ('035 patent, claims 1, 2, 21);
- "little or no serious liver damage" ('428 patent, claim 3); "minimum liver damage, uric acid increases, or elevations in fasting glucose levels" ('848 patent, claim 3);
- "without causing treatment-limiting (i) hepatotoxicity and (ii) abnormalities in uric acid levels or glucose levels or both … which would require said treatment to be discontinued by the patient" ('930 patent, claim 115), and related terms ('930 patent, claims 18, 51, 133; '229 patent, claims 9, 17, 25; '715 patent, clam 1, 5, 9; '691 patent, claim 13; '967 patent, claim 16; '035 patent, claim 1, 2, 21);
- "significant increase in HDL cholesterol" ('848 patent, claim 1); and
- "whereby the capacity of the extended release nicotinic acid to provoke a flushing reaction . . . is reduced or prevented" ('035 patent, claims 1, 21)

1. "effective antihyperlipidemic amount" ('428 patent, claim 1; '930 patent, claims 18, 51, 115, 133; '848 patent, claim 1); "effective

amount of an intermediate release nicotinic acid formulation" ('967 patent, claim 1, 16)

46. In my opinion, a person of ordinary skill in the art in the early to mid-1990s would have understood the claim terms "effective antihyperlipidemic amount" and "effective amount of an intermediate release nicotinic acid formulation" to refer to a therapeutic dose of the drug , *i.e.*, a dose that will have a beneficial effect upon the patient by lowering total cholesterol, LDL cholesterol, triglycerides, and Lp(a) and raising HDL cholesterol.

47. Indeed, the Patents-in-Suit define "effective antihyperlipidemic amount" and "effective amount of an intermediate release nicotinic acid formulation" in terms of niacin's balanced effect on several lipid parameters, which is only obtained when niacin is provided at therapeutic doses:

> an amount which when orally administered to a patient to be treated, will have a beneficial effect upon the physiology of the patient, to include at least some lowering of total cholesterol, LDL cholesterol, triglycerides and Lp(a) and at least some increase in HDL cholesterol in the patient's blood stream.

('428 patent, 3:58-64; '930 patent, 4:7-13; '848 patent, 4:14-20; '967 patent, 17:15-21.)

48. There is no one-size-fits-all dose that produces the desired results in every patient. A physician in the early to mid-1990s would have understood that each patient has to be evaluated individually, and the appropriate dose selected based on his or her age, weight, prior experience with lipid-altering agents, medical history and potential for experiencing side effects, among other things. Nevertheless, a person of ordinary skill in the art in the early to mid-1990s (and subsequently) would have understood that to produce such a beneficial effect upon several lipid parameters in the vast majority of patients would require a daily dose of at least 1 g, and usually more, but not typically more than 3 g. Indeed, the treatment guidelines for physicians set forth in the National Institute of Health's first report of the Expert Panel on

Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults ("ATP I"), published in 1988, stated that a "first-level therapeutic dose" of niacin is between 1.5 g/day and 2 g/day. ATP I, at 55; *see also* National Institutes of Health, "Second Report of the Expert Panel on Detection, Evaluation and Treatment of High Cholesterol in Adults (Adult Treatment Panel II)" (1993), at III-6. The ATP reports were the work of a panel of recognized experts in the field of lipid disorders, and as such were widely regarded as setting the standard of care for treatment of such disorders. Moreover, the label for NIASPAN®, a commercial embodiment of the patents-in-suit, which was approved by the FDA for treatment of hyperlipidemia in 1997, recommends a minimum maintenance dose of 1 g/day.

49. Although the typical therapeutic dose of niacin was 1-3 g/day, it was common practice in the early to mid-1990s to use lower doses of niacin either for nutritional supplementation or, for a short period of time at the outset of niacin therapy, to minimize niacin-induced flushing. As mentioned above, at doses effective for treating hyperlipidemia, niacin causes flushing. Typically, the flushing response is less strong at lower doses of niacin. To manage the flushing response, and to get patients acclimated to the therapy, it is customary to start patients at lower doses of niacin that are sub-therapeutic but that allow them to get used to the flushing response. The daily dose is slowly increased (*i.e.*, titrated) over the course of several weeks to a therapeutic, or maintenance dose. For example, ATP I specifically disclosed that "[n]icotinic acid therapy is generally initiated with a single dose of 100-250 mg/day. This initial dose is usually given after dinner to minimize problems with flushing." ATP I, at 55. Such an initial low titration dose would be gradually escalated in both dose amount and dose frequency to achieve the patient's lipid goal. ATP I, at 55. While the lower doses required for titration may affect some lipid levels in some individuals, it was understood as of 1990 that

such effects were not clinically meaningful. Rather, it was understood that to have a beneficial effect on the physiology of the patient, niacin therapy had to be continued at higher maintenance levels. Therefore, it is my opinion that a person of ordinary skill in the art in the early to mid-1990s would not have understood the use of such sub-therapeutic doses for purposes of minimizing flushing to constitute use of an "effective antihyperlipidemic amount" or an "effective amount of an intermediate release nicotinic acid formulation."

50. I understand that Defendants contend that the terms "effective antihyperlipidemic amount" and "effective amount of an intermediate release nicotinic acid formulation" mean "from about 250 mgs to about 3000 mgs of nicotinic acid." In my opinion, this proposed construction is inconsistent with what a person of ordinary skill in the art in the early to mid-1990s would have understood to be the amount of niacin necessary to produce a beneficial effect across several lipid parameters, including total cholesterol, LDL cholesterol, triglycerides, Lp(a), and HDL cholesterol. As set forth above, the contemporaneous teachings in the literature at that time clearly taught that the usual dose was at least 1 g/day, and that lower doses were to be used for the initial titration stage only, but generally were not sufficient to maintain the beneficial lipid effects of niacin.

2. "effective lipid-altering amount" ('035 patent, claims 1, 2, 21)

51. In my opinion, a person of ordinary skill in the art in the early to mid-1990s would have understood the claim term "effective lipid-altering amount" as used in the '035 patent in much the same way as "effective antihyperlipidemic amount" and "effective amount of an intermediate release nicotinic acid formulation" are used in the '428, '930, '848, and '967 patents (*i.e.*, an amount of niacin that produces a beneficial effect across the several lipid parameters). Thus, a person of ordinary skill in the art in the early to mid-1990s would have

understood the term "effective lipid-altering amount" exactly as the '035 patent defines the term:

> an amount which when orally administered to a patient to be treated, will have a beneficial effect upon the physiology of the patient, to include at least some lowering of; one or more of the following, total cholesterol, LDL-cholesterol, triglycerides and Lp(a) and at least some increase in HDL-cholesterol, and more particularly an increase in, e.g., HDL_2-cholesterol and/or HDL_3-cholesterol, in the patient's blood stream. The beneficial effect will also include some decreases in the total cholesterol to HDL-cholesterol ratio and in the LDL-cholesterol- HDL-cholesterol ratio in the patient's blood stream. In some individuals, the beneficial effect may also include reduction in apolipoprotein B, reduction in apolipoprotein E and/or an increase in apolipoprotein A-I

'035 patent, 12:14-29. Indeed, the only difference between this definition and the definitions of "effective antihyperlipidemic amount" and "effective amount of an intermediate release nicotinic acid formulation" as used in the '428, '930, '848, and '967 patents is the level of detail at which the inventors indentified the affected lipid parameters.

52. I understand that Defendants again contend that this term means "from about 250 mgs to about 3000 mgs of nicotinic acid." I disagree. As discussed above, a person of ordinary skill in the art in the early to mid-1990s (and subsequently) would have recognized that doses of niacin below 1 g/day generally would not have been "effective" at producing a beneficial effect across several lipid parameters. Such doses were used as nutritional supplements or to titrate a patient onto niacin therapy. Defendants' proposed construction for this term, which includes doses less than 1 g/day, is inconsistent with what a person of ordinary skill in the art in the early to mid-1990s would have understood to be necessary to produce a beneficial effect across several lipid parameters that is "effective" in treating hyperlipidemia..

3. "little or no serious liver damage" ('428 patent, claim 3); "minimum liver damage, uric acid increases, or elevations in fasting glucose levels" ('848 patent, claim 3)

53. In my opinion, persons of ordinary skill in the art in the early to mid-1990s, reading the phrase "little or no serious liver damage," would have understood that "***serious*** liver damage" is a side effect requiring discontinuation in treatment (*i.e.*, treatment-limiting hepatotoxicity); otherwise, a person of ordinary skill in the art would not have considered such liver damage "serious."

54. Similarly, a person of ordinary skill in the art in the early to mid-1990s would have understood that "***minimum*** liver damage, uric acid increases, or elevations in fasting glucose levels" to refer to hepatotoxicity (*i.e.*, liver damage) or elevations in uric acid or blood glucose that are not so severe that they require discontinuation of treatment (*i.e.*, no treatment-limiting hepatotoxicity or elevations in uric acid levels or glucose levels which would require effective treatment to be discontinued by the patient); otherwise, a person of ordinary skill in the art would have considered those side effects more serious than "minimum."

55. Of course, "little or no serious liver damage" or "minimum liver damage, uric acid increases, or elevations in fasting glucose levels" does not mean that no such side effects can occur in those using the methods of treatment claimed in the '428 and '848 patents. As an initial matter, these terms are qualified (*i.e.*, "***little*** or no" and "***minimum***"), not absolute, meaning that they contemplate some incidence of these side effects. Moreover, a person of ordinary skill in the art at in the early to mid-1990s (or now) would have understood that no course of therapy is without side effects. Indeed, most therapeutically effective FDA-approved drugs have the possibility of causing an adverse side effect in at least one patient. Anti-cholesterol agents, including statins and fibrates, are particularly known for presenting a risk of liver toxicity. ATP I at 57 (noting "persistent elevations in transaminase levels of greater than

three times the upper limit of normal" for patients taking lovastatin); *id.* at 57-58 ("occasional changes … in liver function tests" have been observed for patients taking gemfibrozil). Accordingly, a person of ordinary skill in the art during the early to mid-1990s would have understood that these claim terms do not require the complete elimination of these side effects.

56. I understand that Defendants contend that these claim terms are indefinite. I disagree. Even though these terms are not susceptible to rigid quantification, a person of ordinary skill in the art in the early to mid-1990s would have understood how to assess whether these side effects were so severe as to be treatment-limiting and require discontinuation of treatment, without undue experimentation.

57. In particular, in light of the long-standing concerns regarding the incidence of liver damage (*i.e.*, hepatotoxicity), increases in uric acid, and elevations in blood glucose, physicians use routine diagnostic tests as benchmarks to assess whether patients taking niacin are experiencing any of these side effects.

58. For example, routine liver function tests, which examine the levels of liver enzymes in a patient's blood, provide a useful benchmark for determining whether a patient is suffering liver damage as a result of niacin therapy. A common endpoint used by the U.S. Food and Drug Administration and clinicians for assessing potential hepatotoxicity is if these liver enzymes exceed three times the upper limit of normal ("ULN"). However, this measure is merely a guidepost, and neither a minimum threshold nor a maximum limit in all cases. On the one hand, a liver function test showing elevations above three times ULN might not necessarily indicate hepatotoxicity requiring discontinuation of niacin treatment. For example, if an individual consumed alcohol prior to testing, it might result in elevated liver enzymes. For this reason, if a patient's liver function test reveals elevated liver enzymes, the doctor is likely to

request additional tests to confirm the results (particularly in the absence of other symptoms of hepatotoxicity). On the other hand, a patient may have liver enzymes lower than three times ULN and yet have other symptoms indicative of hepatotoxicity that may warrant discontinuation of niacin treatment.

59. The tolerable level of liver enzymes for any individual patient depends upon the unique characteristics of that patient, including factors such as the patient's starting level of liver enzymes before treatment, other medical conditions, and personal and family medical history. Based on the results of such tests along with an understanding of these other factors, a clinician experienced in the treatment of lipid disorders would have been able to exercise his or her judgment, guided by training and experience, in deciding whether or not to continue niacin treatment.

60. As with liver function tests, physicians conduct routine blood tests on patients taking niacin to determine whether their uric acid or blood glucose levels are outside the range of normal. The results of these tests are benchmarks for (but not dispositive of) whether the patient is experiencing side effects so severe that treatment should be discontinued. The doctor must evaluate the data in the context of other factors, such as the patient's baseline levels, age, gender, ethnicity, other medical conditions and personal and family medical history, and make a judgment, based on his or her education and training, as to whether or not to discontinue treatment. For example, the doctor may decide, based on all of these factors, that the elevations in uric acid or glucose may be managed through other medications or treatment, and that the disadvantages of withdrawing the patient from niacin treatment outweigh the potential risks posed by the elevated uric acid or glucose levels. It is my opinion that a clinician with

experience in the field of lipid disorders would have been able to exercise his or her judgment, guided by training and experience, in order to make these determinations.

61. Accordingly, a person of ordinary skill in the art would have understood "little or no serious liver damage" to mean "no treatment-limiting hepatotoxicity requiring discontinuation of treatment" (*i.e.*, withdrawal of niacin treatment altogether or a change in the dose administered). Likewise, a person of ordinary skill in the art in the early to mid-1990s would have understood "minimum liver damage, uric acid increases, or elevation in fasting glucose levels" to mean "no treatment-limiting hepatotoxicity or elevations in uric acid levels or glucose levels which would require treatment to be discontinued by the patient."

4. "without causing treatment-limiting (i) hepatotoxicity and (ii) abnormalities in uric acid levels or glucose levels or both … which would require said treatment to be discontinued by the patient" ('930 patent, claim 115)

62. In my opinion, a person of ordinary skill in the art in the early to mid-1990s would have understood the term "without causing treatment-limiting (i) hepatotoxicity and (ii) abnormalities in uric acid levels or glucose levels or both … which would require said treatment to be discontinued by the patient" to refer to hepatotoxicity or abnormalities (*i.e.*, elevations) in uric acid or blood glucose to a level that are significant enough to require discontinuation of treatment. In particular, a person of ordinary skill in the art in the early to mid-1990s would have had a similar understanding of this term as the related terms in the '428 and '848 patents (discussed above). All of these claim terms concern the severity of the side effects caused by niacin therapy, and the only relevant metric for assessing the severity of these various side effects is whether they are so severe as to require the discontinuation of treatment. Accordingly, a person of ordinary skill in the art in the early to mid-1990s would have understood this term to mean "elevations in liver enzymes (AST, ALT and/or alkaline

phosphatase) and either uric acid levels, glucose levels or both to a level that requires discontinuation of current treatment."

63. A person of ordinary skill in the art in the early to mid-1990s (or now) would not have understood that this claim term requires the elimination of the ***risk*** of certain side effects. All drug therapies carry the risk of side effects, and a person of ordinary skill in the art in the early to mid-1990s would have understood that it is not possible to eliminate the risk of side effects entirely. For niacin, in particular, a person of ordinary skill in the art in the early to mid-1990s would have understood that it is not possible to eliminate the risk of hepatotoxicity or abnormalities in uric acid or glucose levels.

64. I understand that Defendants contend that this claim term also is indefinite. I disagree. As discussed above, while there are not quantitative measures that determine definitively whether a patient is experiencing hepatotoxicity or abnormalities in uric acid or glucose that require discontinuation of treatment, a person of ordinary skill in the art in the early to mid-1990s would have used routine tests as a benchmark to assess whether a patient's liver function enzymes, uric acid levels, or blood glucose levels fell outside the range of normal. Based upon the results of these tests, in combination with other factors (*e.g.*, the patient's baseline levels, other medical conditions, family and personal medical history), a person of ordinary skill in the art in the early to mid-1990s would have understood how to determine whether a particular patient is experiencing a treatment-limiting side effect requiring discontinuation of treatment, without undue experimentation.

65. For the same reasons, a person of ordinary skill in the art would have understood the other related claim terms[1] in the Patents-in-Suit concerning "treatment-limiting" side effects to refer to side effect requiring discontinuation of treatment.

5. "significant increase in HDL cholesterol" ('848 patent, claim 1)

66. In my opinion, one of ordinary skill in the art in the early to mid-1990s would have understood that a "significant increase in HDL cholesterol" is any increase that results in a meaningful decrease in the individual's risk of developing cardiovascular disease.

67. Because numerous patient-specific factors influence the onset of cardiovascular disease, whether an individual patient's increase in HDL is "significant" or not will vary from patient to patient. These patient-specific factors include the baseline from which the increase is being measured, the patient's other medical conditions, the patient's personal and family medical history, and any other factors affecting the patient's overall risk of heart disease. As a result, there is no fixed percentage that is recognized in the field as constituting a "significant" increase in HDL. Nevertheless, a person of ordinary skill in the art during the early to mid-

[1] *E.g.*, "without causing drug-induced hepatotoxicity to a level which would require use of said intermediate release nicotinic acid formulation to be discontinued" ('229 patent, claims 9, 17, 25; '715 patent, claim 5); "without causing abnormalities in uric acid levels or glucose levels or both to an extent which would require the use of said release composition by the patient to be discontinued" ('930 patent, claim 18); "without causing abnormalities in either uric acid or glucose levels or both to an extent which would require said daily treatment to be discontinued by the patient" ('930 patent, claim 51); "without causing treatment-limiting myopathy and rhabdomyolysis" ('035 patent, claim 2); "without causing abnormalities in liver function tests and uric acid levels or glucose levels or both to an extent which would require the use of said sustained release composition by the patient to be discontinued" ('930 patent, claim 133); "without causing drug-induced [(i)] hepatotoxicity and (ii) elevations in uric acid or glucose or both, to levels which would require use of said intermediate release nicotinic acid formulation to be discontinued" ('715 patent, claims 1, 9; '691 patent, claim 13); "without causing treatment-limiting hepatotoxicity and treatment-limiting elevations in uric acid or glucose levels or both in the individual to a level which would require use of the intermediate nicotinic acid formulation by the individual to be discontinued" ('967 patent, claim 16); "without causing treatment-limiting hepatotoxicity and elevations in glucose and/or uric acid levels" ('035 patent, claim 1); "without causing treatment-limiting hepatotoxicity, myopathy, rhabdomyolysis and elevations in glucose and/or uric acid levels in the individual" ('035 patent, claim 21).

1990s would have been able to use his or her skill, training, and experience to determine whether an increase in HDL is "significant" for a particular patient.

68. Accordingly, in my opinion, a person of ordinary skill in the art in the early to mid-1990s would have understood that the term a "significant increase in HDL cholesterol" means "an increase that results in a meaningful decrease in an individual's risk of developing cardiovascular disease."

6. "whereby the capacity of the extended release nicotinic acid to provoke a flushing reaction . . . is reduced or prevented" ('035 patent, claims 1, 21)

69. In my opinion, a person of ordinary skill in the art in the early to mid-1990s would have understood the term "whereby the capacity of the extended release nicotinic acid to provoke a flushing reaction . . . is reduced or prevented" to mean whereby there is a reduction in the frequency, duration, or intensity of flushing episodes following administration of the extended release nicotinic acid. In particular, I disagree with defendants' argument that this phrase is indefinite because "flushing is an inherently subjective phenomenon and is also very specific to the individual." (Keenan Rep. ¶ 392.) In my opinion, a person of ordinary skill in the art would have understood the bounds of the claim without undue experimentation.

70. As this case is ongoing, I may supplement the opinions expressed herein at a later date based upon further information provided to me.

I declare under the penalty of perjury that the above is true and correct.

Dated: November 15, 2011

Frank Sacks, M.D.

CURRICULUM VITAE (September 9, 2011)

NAME: Frank M. Sacks

ADDRESS: 129 Leonard Street, Belmont, Massachusetts 02478

PLACE OF BIRTH: Jersey City, New Jersey

EDUCATION:

1970	Biology, Sc.B. Brown University
1970-1972	Music, New England Conservatory of Music
1977	M.D. Columbia University, College of Physicians and Surgeons

POSTDOCTORAL TRAINING:

Internship and Residency:

1977-1978 Resident in Surgery, University Hospital, Madison, Wisconsin

Research Fellowship:

1980-1982 Research Fellow in Medicine, Harvard Medical School and Brigham and Women's Hospital

LICENSURE: 2010- Endocrine Society, Guidelines Panel on treatment of high triglycerides

2010- National Kidney Foundation, KDIGO (Kidney Disease Improving Global Outcomes) Guidelines Committee for treatment of dyslipidemia

1980 Massachusetts

CURRENT APPOINTMENTS:

2000- Professor of Cardiovascular Disease Prevention, Department of Nutrition, Harvard School of Public Health
2004- Professor of Medicine, Harvard Medical School
2004- Senior Physician, Channing Laboratory and Cardiology Division, Brigham & Women’s Hospital

PAST APPOINTMENTS

1992-2004	Associate Professor of Medicine, Harvard Medical School
1992-2004	Physician, Brigham and Women's Hospital
1993-2000	Associate Professor in the Department of Nutrition, Harvard School of Public Health
1992-1993	Assistant Professor in the Department of Nutrition, Harvard School of Public Health
1982-1991	Associate Physician, Brigham and Women's Hospital
1984-1993	Assistant in Medicine, Beth Israel Hospital, Boston
1984-1992	Assistant Professor of Medicine, Harvard Medical School
1982-1984	Instructor in Medicine, Harvard Medical School
1980-1982	Research Fellow in Medicine, Harvard Medical School
1979-1980	Clinical Assistant Professor of Family Practice, University of Wisconsin School of Medicine
1978-1979	Staff Physician, Migrant Health Services, Wild Rose, Wisconsin
1979-1980	Attending Physician, St. Mary's Hospital, Madison, Wisconsin

HONORS AND DISTINCTIONS:

1972	Rockefeller Foundation Award for teaching philosophy of science in the Department of Humanities, New England Conservatory of Music
1974	Annual Prize for Predoctoral Research, Society for Epidemiologic Research
1980-1982	Individual Postdoctoral Research Award, United States Public Health Service
1982-87	Clinician Scientist Award, American Heart Association, Jan Breslow-Preceptor; Edward Kass-Sponsor
1986	Travenol Award Lecture, American College of Nutrition
1987-1992	Established Investigator Award, American Heart Association, Eugene Braunwald, Sponsor
1999	Pierre Bois Lecturer, McGill University and the University of Montreal
2002	Myant Lecturer, British Hyperlipidemia Society
2011	American Heart Association 2011 Research Achievement Award for lifetime research accomplishments

MAJOR PROFESSIONAL SERVICE

1993-97	National Heart, Lung and Blood Institute. Chair, Design and Analysis Committee, Dietary Approaches to Stop Hypertension (DASH) Trial, a multicenter trial on dietary patterns and blood pressure.
1996-2000	National Institutes of Health. Nutrition Study Section
1997-2001	National Heart, Lung, and Blood Institute. Chair, Steering Committee, the Dietary Patterns, Sodium Intake and Blood Pressure trial (DASH2), a multicenter trial.

2000-2011	Organizing Committee and Co-Chair, Lipoprotein Kinetics Conference, Satellite Meeting to the Arteriosclerosis, Thrombosis and Vascular Biology Council Meeting, American Heart Association.
2001	National Cholesterol Education Program, Adult Treatment Panel III, Reviewer of Year 2002 guidelines
2002	NIH, NHLBI: Speaker, Workshop on Lipoprotein (a)
2002	NIH, NHLBI: Workshop participant, Diet and Congestive Heart Failure
2003	NIH, NHLBI: Chair, Committee on 5-year nutrition research agenda
2003	NIH, NHLBI: Member, Committee on 5-year obesity research agenda
2003-07	NIH, NHLBI: Member, DSMB, Gene Environment Interaction Project
2004	NIH, NHLBI: Working group on future clinical research directions on omega-3 fatty acids and cardiovascular disease.
2006	NIH, NHLBI: Consultant group on clinical trial design for lipid drugs
2007-10	American Journal of Clinical Nutrition, Associate Editor
2000-	American Heart Association, Nutrition Committee, Member.
2010-12	American Heart Association, Nutrition Committee, Chair
2008-11	American Heart Association, Leadership Committee, Council on Nutrition Physical Activity and Metabolism
2008-	NCEP ATP-IV: NHLBI Clinical Guidelines for Cardiovascular Risk Reduction, National Cholesterol Education Program ATP-IV Expert Panel member
2008-	Lifestyle Working Group member, NHLBI Clinical Guidelines for Cardiovascular Risk Reduction.
2009	Institute of Medicine, National Academy of Sciences, consultant on treatments for hypertension.
2009	Institute of Medicine, National Academy of Sciences, panel on salt reduction; presented position of the American Heart Association.
2009	United States Dietary Guidelines Panel, invited presentation on diet treatment of obesity and sodium reduction goals.

2009- Residual Risk Reduction Institute: Trustee

2010- Endocrine Society, Guidelines Panel on treatment of high triglycerides

2010- National Kidney Foundation, KDIGO (Kidney Disease Improving Global Outcomes) Guidelines Committee for treatment of dyslipidemia

EDITORIAL BOARDS

Journal of Clinical Lipidology (Associate Editor)
Journal of Lipid Research

MAJOR RESEARCH INTERESTS:

Human lipoprotein metabolism: Kinetic and cell studies on lipoprotein particles that are likely to protect against or to promote atherosclerosis. Effects of diet, apolipoproteins CIII and E. Identification of metabolic pathways in plasma and cells affected by human lipoproteins. Identification of dysfunctional HDL metabolism in humans.

Epidemiology of lipoprotein risk factors for cardiovascular disease: Studies of new lipoprotein subfractions in populations to improve the prediction of cardiovascular disease. These epidemiological studies are linked in scientific scope to the metabolism studies.

Nutritional control of blood pressure and lipid levels: multi-center NIH-NHLBI diet trials. Chair of the DASH-Sodium Steering Committee: “Effects of dietary patterns and sodium intake on blood pressure.” Co-Chair, “Macronutrients and Cardiovascular Risk” (OMNI Heart), a trial of protein, carbohydrate and unsaturated fat to optimize cardiovascular risk factors. Chair of Omni-CARB: “Carbohydrate, type and amount affecting risk of CVD and diabetes”.

Dietary treatment of obesity. PI of multicenter NIH trial (POUNDS LOST) that compared dietary strategies for weight loss.

RESEARCH FUNDING

2003-2009, NIH: 1 UO1 HL073286, F Sacks, PI. Dietary macronutrients and weight loss.

2007-2012, NIH: 1R01 HL084568, F Sacks, PI. Carbohydrate amount and type affecting risk of CVD and diabetes.

2010-2015: NIH, Dietary Fat and HDL Metabolism in Humans. F Sacks, PI.

2009-2010: Harvard Catalyst Program, CTSC NIH award for innovative and translational research: Human HDL metabolism in obesity and dyslipidemia

2009-2011: R3i Foundation grant for an international case-control study of dyslipidemia and both macrovascular and microvascular disease.

PRINCIPAL CLINICAL AND HOSPITAL SERVICE RESPONSIBILITIES:

1984-2010 Hyperlipidemia Clinic, Cardiovascular Division, Brigham and Women's Hospital.

PROFESSIONAL SOCIETIES:

1983- Fellow, Council on Arteriosclerosis, American Heart Association
1983- Fellow, Council on Epidemiology, American Heart Association
1994- Fellow, American Society of Clinical Nutrition
2000- Fellow, Council on Nutrition, Metabolism and Physical Activity, American Heart Association

TEACHING

HARVARD SCHOOL OF PUBLIC HEALTH

1998-2010 The Science of Human Nutrition; Nutritional Biochemistry (NUT202); Course director

2004-2010 Scientific Writing (IS 206), Course director

HARVARD MEDICAL SCHOOL AND TEACHING HOSPITALS

(HMS = Harvard Medical School; BWH = Brigham & Women's Hospital)

1984-2010 Cardiovascular Division Clinic, BWH: clinical teaching of treatment of hyperlipidemia to students, house staff, cardiology fellows and endocrinology fellows

2004-2010 BWH General Internal Medicine faculty: Lectures on hyperlipidemia
1986-2010 BWH CME: Office Practice of Primary Care; Lectures on hyperlipidemia

2005-09 Harvard School of Public Health and Culinary Institute of America, "World of Healthy Eating", workshop for management in the food industry, St.Helena, California

2008 BWH, Cardiovascular Grand Rounds: Apolipoproteins and CVD

2009 BWH, Cardiovascular Grand Rounds: Diet composition to treat obesity

REGIONAL, NATIONAL, OR INTERNATIONAL TEACHING

2011

Tokyo Medical and Dental University: Lecture on diet and cardiovascular disease
National Defense Medical University, Tokorozawa, Japan: Lecture on apoC-III
National Lipid Association, New York: Lecture on diet and weight loss
Gordon Conference on Atherosclerosis, Newport, RI: Lecture on apoC-III

2010

Keystone Conference on Triglycerides: Lecture on apolipoprotein C-III
Quebec Lipidology Society: Lecture on dyslipidemia and residual risk
Beaumont Hospital, Royal Oak, Michigan: Lecture on diet to prevent CVD
American Heart Association Conference on Added Sugars: Lecture on added sugar
Japan Diabetes Association, Okayama, Japan: Lecture on lipid risk factors in diabetes
Karolinska Institute, Stockholm, Sweden: Lecture on diet and cardiovascular disease
Nagoya University, Japan: Lecturer, Conference on Sodium and Hypertension

2009

Medstar CRT symposium, Washington DC, lecture on hypertriglyceridemia
MSDA conference, Berlin, Germany: lecture on apolipoproteins
International Symposium on Atherosclerosis, Boston: lectures on nutrition and obesity
School of Medicine, Universidad de los Andes, Bogota, Columbia: visiting professor
European Society of Cardiology, Barcelona: lecture on lipoprotein risk factors
Metabolic Syndrome Institute conference, Joslin Diabetes Center, Boston
Bari, Puglia, Italy: Conference on Mediterranean diet and health; Lecture on recent science
The Heart.org: Roundtable on genetic markers of cardiovascular risk and response to theapy

2008

Northeast Lipid Association annual meeting, Lecture on hyperlipidemia
American College of Cardiology annual meeting, Lecture on hyperlipidemia
American Diabetes Association annual meeting, Lecture on hyperlipidemia
University of Sydney, Australia, NHMRC clinical trials unit, Lecture on hyperlipidemia

American Heart Association Scientific Sessions, Lecture on postprandial lipoproteins

2007

American Heart Association Scientific Sessions, presenter
Australian Atherosclerosis Society annual meeting, Perth, visiting lecturer
Drugs Affecting Lipid Metabolism conference, New York City, speaker
Metabolic Syndrome Institute meeting, St Petersburg Russia, speaker
University of Texas Southwestern, Dallas, visiting professor
National Lipid Association annual meeting, speaker
European Atherosclerosis Society meeting, Helsinki, speaker
Metabolic Syndrome Diabetes and Atherosclerosis Congress, Lisbon, speaker
American Heart Association, Arteriosclerosis Council meeting, abstract presentation
Insulin Resistance conference, International Diabetes Federation, Barcelona, speaker
American College of Cardiology, annual meeting, speaker
American Heart Association, Epidemiology Council meeting, speaker
Ottawa Heart Institute, grand rounds
St. Michael's Hospital, Toronto, grand rounds
University of California Davis, cardiology grand rounds
National Institutes of Health, inter-institute endocrine grand rounds

2006

American Heart Association, Obesity Conference, 1/2006, speaker
IBC Life Sciences, Metabolic Syndrome Conference, Boston, 3/2006, speaker
University of Washington, Seattle, Cardiovascular Grand Rounds, 4/2006
Columbia University, conference on hypertriglyceridemia, speaker, 4/2006
American Heart Association, Arteriosclerosis Council meeting, presenter, 4/2006
International Atherosclerosis Society meeting, Rome, speaker, 6/2006
European Society of Cardiology meeting, Barcelona, speaker, 9/2006
Biomarkers conference, U Montreal and FDA, Bethesda, panel discussant, 9/2006
NIH, NHLBI, Cardiovascular Knowledge Networks meeting, participant, 9/2006
American Heart Association, Trans Fat conference, Washington, speaker, 10/2006
Cleveland Clinic, conference on obesity, speaker, 10/2006
Cardiometabolic Institute conference, Boston, speaker, 10/2006

American Heart Association, Scientific Sessions, speaker, 11/2006

NIH, NHLBI, Lipid Advisory Panel, participant, 11/2006

American College of Cardiology conference, NYC, speaker, 12/2006

New York Lipid and Vascular Biology Club annual meeting, speaker, 12/2006

BIBLIOGRAPHY:

Peer-Reviewed Journals:

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2. Zinner SH, Martin LF, Sacks FM, Rosner B, Kass EH. A longitudinal study of blood pressure in childhood. Am J Epidemiol 1974;100:437-442.

3. Sacks FM, Castelli WP, Donner A, Kass EH. Plasma lipids and lipoproteins in vegetarians and controls. New Engl J Med 1975; 292:1148-1151.

4. Sacks FM, Donner A, Castelli WP, Gronemeyer J, Pletka P, Margolius HS, Landsberg L, Kass EH. Effect of ingestion of meat on plasma cholesterol of vegetarians. JAMA 1981;246:640-644.

5. Sacks FM, Breslow JL, Wood PG, Kass EH. Lack of an effect of dairy protein (casein) and soy protein on plasma cholesterol of strict vegetarians. An experiment and a critical review. J Lipid Res 1983; 24:1012-1020.

6. Sacks FM, Marais GE, Handysides G, Salazar J, Miller L, Foster JM, Rosner B, Kass EH. Lack of an effect of dietary saturated fat and cholesterol on blood pressure in normotensives. Hypertension 1984; 6:193-198.

7. Sacks FM, Wood PG, Kass EH. Stability of blood pressure levels in vegetarians receiving dietary protein supplements. Hypertension 1984; 6:199-201.

8. Sacks FM, Salazar J, Miller L, Foster JM, Sutherland M, Samonds KW, Albers JJ, Kass EH. Ingestion of egg raises plasma low density lipoproteins in free-living subjects. Lancet 1984;i:647-649.

9. Sacks FM, Ornish D, Rosner B, McLanahan S, Castelli W, Kass EH. Plasma lipoprotein levels in vegetarians. The effect of ingestion of fats from dairy products. JAMA 1985;254:1337-1341.

10. Sacks FM, Handysides GH, Marais GE, Rosner B, Kass EH. The effect of a low fat diet on plasma lipoproteins in normal adults. Arch Intern Med 1986;146:1573-1577.

11. Sacks FM, Breslow JL. Very low density lipoproteins stimulate cholesteryl ester formation in U937 macrophages. Heterogeneity and biologic variation among normal humans. Arteriosclerosis 1987;7:35-46.

12. Sacks FM, Stampfer MJ, Munoz A, McManus K, Canessa M, Kass EH. Effect of linoleic and oleic acids on blood pressure, blood viscosity and erythrocyte cation transport. J Am College Nutr 1987;6:179-185.

13. Sacks, FM, Rouse IL, Stampfer MS, Bishop LM, Lenherr C, Walther RJ. Effect of dietary fats and carbohydrate on blood pressure of mildly hypertensive patients. Hypertension 1987;10:452-460.

14. Sacks FM, Kass EH. Low blood pressure in vegetarians. The effects of specific foods and nutrients. Am J Clin Nutr 1988;48:795-800.

15. Kushi LH, Samonds KW, Lacey JM, Brown PT, Bergan JG, Sacks FM. The association of dietary fat with serum cholesterol in vegetarians: the effect of dietary assessment on the correlation coefficient. Am J. Epidemiol 1988;128:1054-64.

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17. Sacks FM, Creager MA, Gallagher SJ, Loscalzo J, Dzau VJ. Effects of alpha- and beta-adrenergic antagonists on plasma apolipoproteins and forearm blood flow in patients with mild hypertension. Am J Med 1989;86(1B):8-13.

18. Alderman JD, Pasternak RC, Sacks FM, Smith HS, Monrad ES, Grossman W. Effect of a modified, well-tolerated niacin regimen on serum total cholesterol, high density lipoprotein cholesterol and the cholesterol to high density lipoprotein ratio. Am J Cardiol 1989;64:725-9.

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24. Reis GJ, Silverman DI, Boucher TM, Sipperly ME, Horowitz GL, Sacks FM, Pasternak RC. Effects of two types of fish oil supplements on serum lipids and plasma phospholipid fatty acids in coronary artery disease. Am J Cardiol 1990: 66:1171-1175.

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ABBOTT LABORATORIES and ABBOTT RESPIRATORY LLC, Plaintiffs, v. TEVA PHARMACEUTICALS USA, INC. and TEVA PHARMACEUTICAL INDUSTRIES LTD., Defendants.	C.A. No. 10-00057 (SLR)(MPT) CONSOLIDATED

ABBOTT LABORATORIES and ABBOTT RESPIRATORY LLC, Plaintiffs, v. WATSON LABORATORIES, INC.-FLORIDA, Defendants.	

DECLARATION OF ROBERT O. WILLIAMS III, PH.D.
IN SUPPORT OF PLAINTIFFS' OPENING CLAIM CONSTRUCTION BRIEF

I, Robert O. Williams III, Ph.D., submit this declaration in support of the Claim Construction Brief of plaintiffs Abbott Laboratories and Abbott Respiratory LLC ("Abbott").

I. INTRODUCTION

1. I have been retained by Abbott to provide expert opinions and testimony in the above-captioned case. I understand that Abbott has filed suit against Teva Pharmaceutical Industries, Ltd. and Teva Pharmaceuticals USA, Inc. (collectively, "Teva") and has alleged that Teva's filing of Abbreviated New Drug Application ("ANDA") No. 20-0478 ("Teva's ANDA") for the approval of generic versions of Abbott's drug SIMCOR® infringes certain identified claims of U.S. Patent Nos. 6,080,428 ("the '428 patent"), U.S. Patent No. 6,129,930 ("the '930 patent"), U.S. Patent No. 7,011,848 ("the '848 patent"), U.S. Patent No. 6,818,229 ("the '229 patent"), U.S. Patent No. 6,406,715 ("the '715 patent"), U.S. Patent No. 6,676,967 ("the '967 patent"), U.S. Patent No. 6,746,691 ("the '691 patent"), and U.S. Patent No. 6,469,035 ("the '035 patent") (collectively, the "SIMCOR® Patents").

2. I also understand that Abbott has filed suit against Watson Laboratories, Inc. – Florida ("Watson") and has alleged that Watson's filing of ANDA No. 20-0601 ("Watson's ANDA") for the approval of generic versions of Abbott's drug SIMCOR® infringes certain identified claims of the SIMCOR® patents.

3. I have been asked to provide some background regarding drug formulation technology. In addition, I have been asked to comment on the meaning of certain terms in the claims of the SIMCOR® patents from the perspective of one of ordinary skill in the art in the mid-1990's.

II. BACKGROUND

4. I am currently the Johnson & Johnson Centennial Professor of Pharmaceutics and Head of the Division of Pharmaceutics in the College of Pharmacy at the University of Texas at Austin. I have an undergraduate degree in biology from Texas A&M University and a Bachelor of Science in Pharmacy degree from the University of Texas at Austin. I am a licensed pharmacist. I received a doctorate degree in Pharmaceutics from the University of Texas at Austin in 1986.

5. After receiving my doctorate, I worked in the pharmaceutical industry for about nine years, including at Eli Lilly and Company, Duramed Pharmaceuticals, and Rhone-Poulenc Rorer. I have worked in the area of research and development of pharmaceutical formulations since about 1986. I have extensive experience in designing, developing, and analyzing drug delivery systems in various types of dosage forms, including tablets prepared by dry granulation and wet granulation techniques. I have extensive experience developing modified release drug formulations from about 1984 to the present (e.g., delayed release and sustained release). I also have extensive experience in characterization of modified release drug formulations, including using dissolution testing.

6. In 1995, I became an Assistant Professor of Pharmaceutics in the College of Pharmacy at the University of Texas at Austin. In 1999, I became an Associate Professor of Pharmaceutics, and in 2004, a Professor of Pharmaceutics. At the University of Texas at Austin, I teach courses at the undergraduate and graduate level in pharmaceutics, product development, pharmaceutical processing, and manufacturing pharmacy. Specifically, these courses include topics related to dosage form development (e.g., immediate release and modified release solid oral dosage forms, such as tablets).

7. From January 1996 to January 2007, I was the President of PharmaForm, LLC in Austin, Texas, a contract pharmaceutical services company. From January 2007 – June 2010, I served as a consultant to PharmaForm, LLC. During this time period, I also served on the Board of Directors of Akela Pharma, Inc. Since November 2009, I have served as Chief Scientist for Enavail LLC, a particle engineering and drug delivery pharmaceutical company, which is located in Austin, Texas. My role in each of these companies generally involved drug formulation and dosage form development.

8. I was elected Fellow of the American Association of Pharmaceutical Scientists (AAPS) in 2006, and Fellow of the American Institute for Medical and Biological Engineering (AIMBE) in 2008. I have authored or co-authored over 300 published, peer-reviewed articles, abstracts, and book chapters. I have published numerous articles relating to dosage form development and characterization. I have co-edited one book on the topic of drug formulation and have a second book on a similar topic that will be published in Fall 2011. I am a co-inventor on over 20 patents and patent applications, the majority of which relate to pharmaceutical technology. Most of these patents concern drug delivery, and many concern drug dissolution and bioavailability. I have given numerous invited lectures world-wide on various topics in pharmaceutics. I am editor-in-chief of *Drug Development and Industrial Pharmacy* (Informa Healthcare, publisher) and serve as a reviewer for other peer-reviewed journals in my field of expertise.

9. My curriculum vitae is attached as Exhibit A.

III. BACKGROUND OF PHARMACEUTICAL FORMULATIONS

10. A “dosage form” includes one or more active ingredients, and other pharmacologically inert ingredients.

11. The amount of active ingredient in the dosage form determines its tablet strength. For example, in the case of niacin, a 500 mg tablet contains approximately 500 milligrams of nicotinic acid. The tablet strength is not necessarily the same thing as the dose. A specified dose of a drug may require administration of one or more tablets of a given tablet strength.

12. The inert ingredients in a particular dosage form are typically referred to as "excipients." An excipient may be included in a tablet dosage form to add color, improve taste, affect the drug release rate, improve stability, act as a processing aid, enhance the physical properties of the tablet, and/or to perform other functions related to the delivery of the active ingredient.

13. An example of an excipient is a binder or binding agent. Such an excipient is typically used to aid in tablet production. A binder is mixed with and imparts cohesive qualities to the powdered materials that are compounded together and compressed to form a tablet. The binder thus serves to ensure that the tablet remains intact after compression. Common binders include polyvinyl pyrollidone, also known as povidone, and starch.

14. Another example of an excipient is a swelling agent. When the dosage form is ingested, a swelling agent will gradually swell in the patient's gastrointestinal tract, and release the active ingredient into the gastrointestinal system for absorption into the blood stream. A swelling agent may be used to control the release of the active ingredient, and thereby to provide a sustained release formulation. Common swelling agents include polymers, such as hydroxypropyl methylcellulose, hydroxypropyl cellulose, and sodium carboxymethylcellulose; gums, such as sodium alginate and xantham gum; polyethylene oxide; and gelatins.

15. Another example of an excipient is a lubricant, which is typically used as a tableting aid to reduce friction between (i) the tablet punches and the die during tablet compression and ejection, and (ii) the outer surface of a tablet and the surfaces of the die cavity and the tablet press. The lubricant is blended with the active ingredient and other excipients prior to formation of the tablet. Common lubricants include magnesium stearate, stearic acid, and hydrogenated vegetable oils.

16. When a drug product is specified as having a particular percentage of an excipient by weight—such as 1 part by weight of binder per 100 parts by weight of tablet—that does not necessarily mean that it contains exactly 1% binder by weight. As in any manufacturing process, there is some variability in the amount of binder that goes into the blend or that might be lost during the tableting process, as a result of factors such as the tolerances of the equipment being used to measure the material, the tolerances of the various pieces of equipment that may be used to process the tablet, and the accuracy of the technicians handling the material and equipment.

17. Likewise, when a drug product is specified as having a particular percentage range of an excipient by weight—such as from about 1 to about 4 parts by weight of binder per 100 parts by weight of tablet—that does not necessarily mean that it contains exactly between 1% and 4% binder by weight. This is due to the inherent variabilities that are part of any manufacturing process, discussed above.

IV. OPINION

A. Person Of Ordinary Skill In The Art

18. I understand that for purposes of construing the disputed claim terms, it is necessary to examine those terms from the view point of a person of ordinary skill in the art at the time of the invention.

19. In my opinion, the arts relevant to the SIMCOR® Patents are the design, formulation, and testing of oral solid dosage forms; biopharmaceutics and pharmacokinetics; and the treatment of patients with lipid disorders.

20. In my opinion, a person of ordinary skill in the art with respect to the SIMCOR® Patents in the 1990s would have basic knowledge of solid oral dosage formulation, biopharmaceutics and pharmacokinetics, and the treatment of lipid disorders, either through experience working in drug development and formulation or through training (such as a degree in pharmacy or a medical degree), and several years of experience or training in one or more of the relevant arts.

B. Disputed Claim Terms

21. I have been asked to provide my opinion regarding the understanding of a person of ordinary skill in the art in the mid 1990s regarding the following terms:

- binder (’428 patent, claim 6; ’930 patent, claims 19, 24, 28, 134, 139, 143; and ’848 patent, claim 6)
- processing aid (’930 patent, claims 19, 25, 29, 134, 140, 144)
- lubricant (’930 patent, claims 25, 26, 140, 141, 144)
- about (’428 patent, claim 6; ’930, claim 143; and ’848 patent, claim 6)

1. *Binder*

22. In my opinion, in the context of the ‘428, ‘930, and ‘848 patents, a person of ordinary skill in the art would have understood the term “binder” to mean a material that is

mixed with and imparts cohesive qualities to the powdered materials that are compounded together and compressed to form a tablet which ensures the tablet remains intact after compression.

23. The ‘428, ‘930, and ‘848 patents discuss three “test tablet compositions” where nicotinic acid is combined with a binder (povidone), a swelling agent (hydroxypropyl methylcellulose), and a processing aid or lubricant (stearic acid). (‘428 patent, col. 4, l. 4-col. 5, l. 13; ‘930 patent, col. 4, l. 5-col. 5, l. 21; ‘848 patent, col. 4, l. 12-col. 5, l. 33.) The patents further state: “The ingredients were compounded together to form a tablet.” (‘428 patent, col. 5, ll. 12-13; ‘930 patent, col. 5, ll. 20-21; ‘848 patent, col. 5, ll. 32-33.) A person of ordinary skill in the art would understand that the ingredients of the test tablet composition, including the binder, are mixed together prior to tablet compression.

24. The ‘930 and ‘848 patents further discuss the Niaspan® tablet formulations, as well as the process for manufacturing Niaspan® tablets. (‘930 patent, col. 6, l. 1-col. 8, l. 32; ‘848 patent, col. 6, l. 4-col. 8, l. 50.) The patents state, “Povidone K90 is employed as a granulating/binding agent ***in a Niaspan® formulation***.” (‘930 patent, col. 5, ll. 46-47; ‘848 patent, col. 5, ll. 57-58) (emphasis added). Furthermore, the patents state that the povidone binder is mixed together with the niacin, Methocel E10M, and stearic acid prior to compression to form a tablet. (‘930 patent, col. 6, l. 56-col. 7, l. 10; ‘848 patent, col. 6, l. 40-col. 7, l. 18.) A person of ordinary skill in the art would understand the patents as describing the mixing of various powdered components, including a binder, and the subsequent compression of the mixture to form tablets. A skilled artisan would understand, therefore, that the binder imparts cohesive qualities to this mixture to ensure that the tablet remains intact after compression.

25. Several publications known in the art support my opinion that a person of ordinary skill in the art would have understood the term "binder" to mean a material that is mixed with and imparts cohesive qualities to the powdered materials that are compounded together and compressed to form a tablet which ensures the tablet remains intact after compression. For instance, *Remington's Pharmaceutical Sciences* defines "binders" as:

> Agents used to impart cohesive qualities to the powdered material are referred to as binders or granulators. They impart a cohesiveness to the tablet formulation which insures the tablet remaining intact after compression, as well as improving the free-flowing qualities by the formulation of granules of desired hardness and size.

Remington's Pharmaceutical Sciences (1985) at 1605 (emphasis added). Similarly, *The Theory and Practice of Industrial Pharmacy* describes the use of binders in wet granulation processes:

> Wet granulation forms the granules by binding the powders together with an adhesive, instead of by compaction. The wet granulation technique employs a solution, suspension, or slurry containing a binder, which is usually added to the powder mixture; however, the binder may be incorporated dry into the powder mix, and the liquid may be added by itself.

Leon Lachman *et al.*, *The Theory and Practice of Industrial Pharmacy*, 3d ed. (1986) at 320 (emphasis added). The *Handbook of Pharmaceutical Granulation Technology* also discusses the use of binders to provide a cohesiveness to hold tablets together after compression:

> Binders are adhesives that are added to the tablet formulations. The role of binders is to provide the cohesiveness essential for the bonding of the solid particles under compaction to form a tablet.

Rajendra K. Khankari *et al.*, "Binders and Solvents," *Handbook of Pharmaceutical Granulation Technology*, 1st ed. (1997) at 60. The *Handbook of Pharmaceutical Excipients* discusses the binder povidone: "In tableting, povidone solutions are used as binders in wet granulation processes. Povidone is also added to powder blends in the dry form and granulated *in situ* by the

addition of water, alcohol, or hydroalcoholic solutions." *Handbook of Pharmaceutical Excipients,* at 392 (1994). The *Handbook of Pharmaceutical Excipients* characterizes povidone as a "suspending agent [and] tablet binder." *Id.*

26. I understand Defendants contend that a binder is "a material used to hold the ingredients of the tablet together, and/or to give the tablet strength." In my opinion, Defendants' construction is overly broad and potentially covers materials that one of ordinary skill in the art would not consider to be a binder in the context of the '428, '848, and '930 patents. As explained above, a person of ordinary skill in the art would understand the term "binder" in the context of the '428, '848, and '930 patents to mean a material that is mixed with other excipients prior to compression of the tablet. Defendants' construction, however, could improperly cover materials that hold the ingredients of the tablet together externally, such as external coatings.

27. I further understand Defendants contend that for the '930 patent, a binder must "provide sustained release." I disagree. A person of ordinary skill in the art would not understand the term "binder" to mean a compound that, generally speaking, prolongs the release of the active ingredient in a tablet. For example, according to *Polyvinylpyrrolidone Excipients for Pharmaceuticals,* povidone does not act to control the release of active ingredient in sustained release formulations: "Because of its excellent solubility, povidone normally has no delaying effect on the dissolution of active substances. Though a substance embedded in povidone K 90 dissolves slightly more slowly than it would in povidone K 30, this minor difference cannot be described as a controlled-release effect." V. Buhler, *Polyvinylpyrrolidone Excipients for Pharmaceuticals: Povidone, Crospovidone and Copovidone* (2005) at 113. The preferred embodiments of the '930 patent, *i.e.*, Niaspan® tablets, all contain Povidone K90. Furthermore, the specification of the '930 patent nowhere states that a binder provides sustained

release. The specification instead states that the swelling agent (e.g., hypromellose) provides sustained release. ('930 patent, col. 4, ll. 22-28.)

28. Therefore, in my opinion, the term "binder" means a material that is mixed with and imparts cohesive qualities to the powdered materials that are compounded together and compressed to form a tablet which ensures the tablet remains intact after compression. My understanding of this term would have been the same in the mid-1990s, and, in my opinion, would have been shared by a person of ordinary skill in the art at that time.

2. *Processing Aid*

29. In my opinion, a person of ordinary skill in the art would have understood the term "processing aid" to mean its plain and ordinary meaning, *i.e.*, a material used to aid processing of the tablet.

30. I understand Defendants contend that for the '930 patent, a processing aid must "provide sustained release." I disagree. A person of ordinary skill in the art would not understand the term "processing aid" to mean a compound that, generally speaking, prolongs the release of the active ingredient in a tablet. Furthermore, the specification of the '930 patent nowhere states that a processing aid provides sustained release. The specification instead states that the swelling agent (e.g., hypromellose) provides sustained release. ('930 patent, col. 4, ll. 22-28.)

3. *Lubricant*

31. In my opinion, a person of ordinary skill in the art would have understood the term "lubricant" to mean its plain and ordinary meaning, *i.e.*, a material used to provide lubrication.

32. I understand Defendants contend that for the '930 patent, a lubricant must "provide sustained release." I disagree. A person of ordinary skill in the art would not understand the term "lubricant" to mean a compound that, generally speaking, prolongs the release of the active ingredient in a tablet. Furthermore, the specification of the '930 patent nowhere states that a lubricant provides sustained release. The specification instead states that the swelling agent (e.g., hypromellose) provides sustained release. ('930 patent, col. 4, ll. 22-28.)

4. *About*

33. I understand that the parties disagree over the interpretation of the term "about" in the asserted claims of the '428, '930, and '848 patents. Below is a side-by-side comparison of the parties' respective constructions of the disputed terms in the applicable claims:

Claim Term	Abbott's Proposed Construction	Defendants' Proposed Construction
"from about 1 to about 4 part by weight of binder per 100 parts by weight of tablet" ('428 patent, claim 6; '848 patent, claim 6)	The amount of [binder] is from approximately 1% to approximately 4% of the weight of the tablet.	The amount of [binder] must be no less than 0.5% and no more than 4.4% of the weight of the tablet
"from about 1% to about 5% part by weight of binder per 100 parts by weight of tablet" ('930 patent, claims 28, 143)	The amount of [binder] is from approximately 1% to approximately 5% of the weight of the tablet.	The amount of [binder] must be no less than 0.5% and no more than 5.4% of the weight of the tablet

34. These claim terms in the ‘428, ‘930, and ‘848 patents relate to percentage by weight of binder when measured against the weight of the tablet. As I explained in Paragraph 17 above, the specified range of percentage of binder reflects the ideal amount of binder in the formulation. However, due to the inherent variability in the manufacturing process, the actual amount of binder in the formulation may vary slightly. In my opinion, the use of “about __%” and “about __ parts by weight per 100 parts by weight” in the context of the ‘428, ‘930, and ‘848 patents is intended to reflect and allow for such variability. Therefore, in my opinion, a person of ordinary skill in the art would have understood these phrases to mean “approximately __ %” or “approximately __ parts by weight per 100 parts by weight,” respectively.

35. I understand that Defendants contend that the use of the language “about __%” or “about __ parts by weight per 100 parts by weight” should be interpreted as imposing a numerical range of ± 0.5%. I disagree. I am not aware of any reference to such a numerical range in the ‘428, ‘930, or ‘848 patents and, therefore, in my opinion, a person of ordinary skill in the art reading those patents would not understand that the inventors intended to adopt such a specific range with their use of the phrases “about __%” and “about __ parts by weight per 100 parts by weight.”

36. As this case is ongoing, I may supplement the opinions expressed herein at a later date based upon further information provided to me.

I declare under penalty of perjury that the above is true and correct.

Dated: November 15, 2011

Robert O. Williams III, Ph.D.

Exhibits

Exhibit A Curriculum Vitae

CURRICULUM VITAE
Robert O. (Bill) Williams III

Office Address
The University of Texas at Austin
College of Pharmacy
Division of Pharmaceutics
2409 University Ave., Room 4.214
1 University Station A1920
Austin, Texas 78712
Office (512)471-4681 Fax (512)471-7474
Email: williro@mail.utexas.edu

Home Address
4514 West Rapid Springs Cove
Austin, Texas 78746
(512)306-8396

I. Personal

Born September 11, 1956 in Beaumont, Texas. Citizen of the United States. Married; two children.

II. Education

May 75 – May 79	Texas A&M University, College Station, Texas Bachelor of Science in Biology, Graduated with special honors
Sep 79 – Dec 81	University of Texas at Austin, Austin, Texas. Bachelor of Science in Pharmacy, Graduated with special honors Registered Pharmacist – State of Texas
Aug 82 – May 86	University of Texas at Austin, Austin, Texas Doctor of Philosophy, Pharmaceutics Major Professor: James W. McGinity, Ph.D.

III. Positions Held

1. January, 1982 to August, 1982 – Registered, Pharmacist, Walgreen's Pharmacy, Beaumont, TX.
2. August, 1986 to December, 1988 - Group Leader for Eli Lilly and Company, Indianapolis, IN.
3. January, 1989 to December, 1990 - Director for Duramed Pharmaceuticals, Cincinnati, OH.
4. January, 1991 to April, 1992 - Section Manager for Rhone-Poulenc Rorer Pharmaceuticals, Collegeville, PA.

5. April, 1992 to January, 1993 - Department Manager for Rhone-Poulenc Rorer Pharmaceuticals, Collegeville, PA.
6. January, 1993 to August, 1995 - Director for Rhone-Poulenc Rorer Pharmaceuticals, Collegeville, PA.
7. September, 1995 to August, 1999 - Assistant Professor of Pharmaceutics, College of Pharmacy, University of Texas at Austin, Austin, TX.
8. January, 1996 to January, 2007 – President, PharmaForm LLC, Austin, TX.
9. January, 2007 – June, 2010 – Consultant, PharmaForm LLC, Austin, TX.
10. January, 2007 to June, 2010 – Board of Directors, Akela Pharma, Inc., Montreal, Canada
11. September, 1999 to August, 2004 – Associate Professor of Pharmaceutics, College of Pharmacy, University of Texas at Austin, Austin, TX.
12. September, 2004 to present – Professor of Pharmaceutics, Johnson & Johnson Centennial Professor, College of Pharmacy, University of Texas at Austin, Austin, TX.
13. September, 2007 to present – Division Head, Division of Pharmaceutics, College of Pharmacy, University of Texas at Austin, Austin, TX.
14. Founder and Chief Scientist, Enavail LLC, 2009-present, Austin, TX.

IV. Graduate and Undergraduate Courses Presented

Pharmaceutics, PHR 356C and PHR 156P - UT Austin
Advanced Manufacturing Pharmacy, PHR 381G - UT Austin
Recent Advances in Pharmaceutics, PHR 382R - UT Austin
Advanced Product Development, PHR 381D - UT Austin
Advanced Pharmaceutical Processing, PHR 380Q - UT Austin

V. Professional Memberships

American Association of Pharmaceutical Scientists 1985 - present
(Sections of Pharmaceutical Technology, and Pharmaceutics and Drug Delivery)
- Member, Planning Committee, Pharmaceutical Technology Section (1997-1998)
- Member, Strategic Planning Committee (1999-2000)
- Reviewer, Pharmaceutical Technology Screening Committee (2003, 2004)
- Co-Chair, Strategic Visioning Process (2003-2004)
- Reviewer, Annual Meeting and Exposition Abstract Screening Committee (2006)
- Member, Pharmaceutical Technology Education Committee (2007-present)

Controlled Release Society 1995 - present
Association de Pharmacie Galenique Industrielle (APGI) 1998 - present
American Association of Colleges of Pharmacy 1995 - present
Rho Chi (Pharmacy Honor Society) 1982 - present
Kappa Psi (Graduate Chapter, Pharmacy Professional Fraternity), 1979 - present

Grand Council Deputy - President	1998 – present
International Academy of Compounding	1999 – 2004
European Federation of Biotechnology	2002 – present
Product Quality Research Institute	2004 – 2005
(AAPS representative on Drug Product Technical Committee)	
Center for Microencapsulation and Drug Delivery,	2003-present
Texas A&M University (Member – Strategic Advisory Board)	

VI. Current Research Interests

1. Small particle technology to enhance dissolution rates and bioavailability.

2. Formulation of novel liquid and semisolid drug delivery systems.

3. Study of novel controlled-release aqueous coating formulations.

4. Preformulation and formulation of novel delivery systems for pulmonary, nasal and buccal delivery.

5. Peptide and protein delivery; analytical characterization of peptides and proteins.

VII. Honors and Awards

1. University Undergraduate Honors Fellow, Texas A&M University; 1978

2. Distinguished Student Award, Texas A&M University; 1979

3. Lemmon Award, University of Texas at Austin; 1981

4. Amaric Corporation Pre-doctoral Fellowship, University of Texas at Austin; 1983 - 1985

5. Professional Development Award, University of Texas at Austin; 1985

6. Texas Excellence Teaching Award, University of Texas at Austin; 1998

7. Phi Lambda Sigma, the Pharmacy Leadership Society, Elected member - 1998

8. Leadership Fellow, American Association of Colleges of Pharmacy Academic Leadership Fellows Program, 2004-2005.

9. Paper awarded the Penwest Award for Best Scientific Paper, Novel Curing Process for Cellulose Acetate Phthalate Coated Beads. Proceedings of the 20th Pharmaceutical Technology Conference and Exhibition, Liverpool, UK, April, 2001.

10. Dean's Fellow, College of Pharmacy, University of Texas at Austin, 2004-2005.

11. Fellow, Elected by the American Association of Pharmaceutical Scientists, 2006.

12. Paper awarded the Controlled Release Society's Innovative Aspects of Oral Drug Delivery and Absorption Graduate/Post-Doc Award, Improved Dissolution Rate and Bioavailability Through the Formation of a Highly Miscible Binary Mixture, Proceedings of the Controlled Release Society Annual Meeting, Miami, FL, June, 2005.

13. Paper nominated for the Controlled Release Society's Innovative Aspects of Oral Drug Delivery and Absorption Graduate/Post-Doc Award, Rapid Release, High Potency Itraconazole Formed by Evaporative Precipitation Into Aqueous Solution, Proceedings of the Controlled Release Society Annual Meeting, Miami, FL, June, 2005.

14. Outstanding Thesis Award, Barbara Jean Hoeben, M.S. (May, 2005) – Thesis Title: Comparison of Commercial Itraconazole to Aerosolized Nanoparticle Itraconazole in a Murine Model for the Prevention of Invasive Pulmonary Aspergillosis (IPA).

15. Elected "Fellow" of the American Association of Pharmaceutical Scientists, 2006.

16. Elected "Fellow" of the American Institute of Medical and Biological Engineering, 2008.

17. Received the 2009 William J. Sheffield Outstanding Alumnus Award, Pharmacy Alumni Association, The University of Texas at Austin.

18. Invited paper by W. Yang, J. I. Peters and R. O. Williams III was recognized as one of the Top-10 most cited articles published in *International Journal of Pharmaceutics* during the period 2008-2010 (Elsevier Publishers; September 2010).

VIII. Committees

Academic Performance Committee - 1996 – present, Chairman and Member
Faculty Retreat Planning Committee, Chair - 1996-1997, 2007, 2011
Committee on Committees - 1995 – 1997, 2004 – 2005, 2006
Pharmacy Honors Course - Coordinator for Pharmaceutics - 1996 - 2001
Honors and Awards Committee - 1995 - 2001
Internship Region Assignment Committee, Chairman, 1998 - 2004
Staff Excellence Awards Committee - 1998 – 2000
Financial Aid Committee – 1999 – 2000

College Accreditation Committee – 2002 – present
Admissions and Registration Committee (University Committee) – 2001 – 2003
Intellectual Property Committee (University Committee) – 2003- present
Co-Chair – Life Sciences (2004-2005)
Faculty Advisor to: Kappa Psi Pharmaceutical Fraternity
Pharmaceutical Association of Compounding
Drug Product Technical Committee, PQRI – representative for AAPS, 2004-2006
Post-Tenure Review Committee – Chairman; 2005-2007
College of Pharmacy, Dean Search Committee – Co-Chairman; 2007
College of Pharmacy, Executive Committee – Chairman; 2008 – present
University of Texas at Austin, Office of Technology Commercialization and Associate Vice President for Research for Commercialization Search Committee; 2008-2010
Graduate Studies Committee, Pharmacy Doctoral Program (1995 – present)
Graduate Studies Committee, Translational Science Doctoral Program (2011-present)

IX. Editorial Responsibilities

1. *Drug Development and Industrial Pharmacy* – Editor-in-Chief (2000 – present)
2. *International Journal of Pharmaceutics* - reviewer
3. *Pharmaceutical Research* - reviewer
4. *European Journal of Pharmaceutics and Biopharmaceutics* - reviewer
5. *Journal of the Controlled Release Society* - reviewer
6. *S. T. P. Pharma. Sciences* - reviewer
7. *Pharmaceutical Development and Technology* - reviewer
8. Pharmaceutical Technology Conference - International Advisory Board Member
9. *International Journal of Pharmaceutical Compounding* – reviewer
10. *Journal of Membrane Science* – reviewer
11. *AAPS PharmSciTech* – reviewer
12. *Journal of Pharmaceutical Sciences* – reviewer
13. *Journal of Pharmaceutical and Biomedical Analysis* – reviewer
14. *Toxicology Letters* – reviewer

15. National Institutes of Health, National Institute of Allergy and Infectious Diseases, *Pharmaceutical and Chemical Resources for AIDS Drug Development*, invited reviewer.

16. *The Open Drug Delivery Journal*, Member, Editorial Advisory Board, 2008-present.

17. *Journal of Pharmaceutical Research & Clinical Practice*, Editorial Advisory Board, 2010-present.

X. Students Currently Being Supervised

Kevin O'Donnell – Ph.D.
Nicole Nelson – Ph.D.
Stephanie Bosselmann – Ph.D.
Bo Lang – Ph.D.
Helene Lirola – Ph.D.
Yi-Bo Wang – Ph.D.
Meimei Zhang – Ph.D.
Houli Li – Ph.D.

XI. Personnel Supervised (and Starting Position; if available)

1. Mongkol Sriwongjanya, Ph.D. (1996 – 1997; Post-doctoral Research Fellow) Senior Research Scientist, Andrx Pharmaceuticals, Fort Lauderdale, FL

2. Jie Liu, Ph.D. (August, 1998) Senior Research Scientist, Baxter Healthcare, New Providence, NJ. Dissertation Title: Development, Characterization and Optimization of Pressurized Metered-Dose Inhalers Formulated to Delivery Small Organic Drugs or Proteins with Hydrofluoroalkane Propellants.

3. Chengjiu Hu, Ph.D. (August, 1999) Senior Research Scientist, DuPont Pharmaceuticals, Garden City, NY. Dissertation Title: Investigation of Factors Influencing the Development of Pressurized Metered Dose Inhalers.

4. Melisa K. Barron, Ph.D. (August, 2000) Senior Scientist, Dey Laboratories, Napa, CA. Dissertation Title: Investigation of Formulation and Processing Technique on the Characteristics of Polymeric Powders Produced for Suspension Type Pressurized Metered Dose Inhalers Systems.

5. Jiping Liu, Ph.D. (August, 2001) Research Investigator, Sanofi-Synthelabo, Philadelphia, PA. Dissertation Title: Applications of Cellulose Acetate Phthalate Aqueous Dispersion (Aquacoat CPD) for Enteric Coating.

6. Bobby J. Truong, M.S. (August, 2001). Thesis Title: Development of Insulin Pressurized Meter-Dose Inhaler for the Pulmonary Drug Delivery by Spray-Freezing into Cryogenic Vapor.

7. Marazban Sarkari, Ph.D. (2000-2001; Post-doctoral Research Fellow) Senior Scientist, RxKINETIX, Boulder, CO

8. Vorapann Mahaguna, Ph.D. (December, 2001) Senior Research Scientist, DuPont Pharmaceuticals, Garden City, NY. Dissertation Title: Investigation of Cellulose Ether Polymers in Controlled Drug Delivery.

9. Raouf Ghaderi, Ph.D. (2001-2002; Post-doctoral Research Fellow) Senior Research Scientist, KOS Pharmaceuticals, NJ

10. True L. Rogers, Ph.D. (June, 2002) Senior Research Scientist, The Dow Chemical Company, Midland, MI. Dissertation Title: A Novel Cryogenic Particle Engineering Technology to Micronize Water-Insoluble Drugs and Enhance Their Dissolution Properties: Spray-Freezing Into Liquid.

11. Jiahui Hu, Ph.D. (July, 2003) – Senior Research Scientist, Forest Laboratories, Garden City, NY. Dissertation Title: A Nanoparticle Engineering Process: Spray-Freezing into Liquid to Enhance the Dissolution of Poorly Water Soluble Drugs.

12. Bradi L. Jones, Pharm.D., M.S. (August, 2003) – Pharmacist, University of Texas Health Science Center at San Antonio, San Antonio, TX. Thesis Title – Investigation of Pulmonary and Oral Delivery of Itraconazole Produced by Evaporative Precipitation into Aqueous Solution and Spray Freezing into Liquid Technology in a Murine Model.

13. Thomas W. Leach, Ph.D. (2002-2004 – Post-doctoral Research Fellow) Senior Research Scientist, Curagen Inc., New Haven, CT

14. Zhongshui Yu, Ph.D. (July, 2004) – Senior Research Scientist, Hoffmann-La Roche Pharmaceuticals, Nutley, NJ. Dissertation Title: Spray Freezing into Liquid to Produce Protein Microparticles.

15. Xiaoxia Chen, Ph.D. (July, 2004) – Senior Research Scientist, Hoffmann-La Roche Pharmaceuticals, Nutley, NJ. Dissertation Title: Nanoparticle Engineering Processes: Evaporative Precipitation into Aqueous Solution (EPAS) and Anitsolvent Precipitation to Enhance the Dissolution Rates of Poorly Water Soluble Drugs.

16. Thiago Cardoso Carvalho, R.Ph. (July, 2004) – Visiting Scientist, Universidade Federal De Minas Gerais, Brazil.

17. Barbara Jean Hoeben, M.S. (May, 2005) – Pharmacist, United States Air Force, San Antonio, TX. Thesis Title: Comparison of Commercial Itraconazole to Aerosolized Nanoparticle Itraconazole in a Murine Model for the Prevention of Invasive Pulmonary Aspergillosis (IPA).

18. Jason M. Vaughn, Ph.D. (June, 2005) – Associate Director and Senior Research Scientist, PharmaForm LLC, Austin, TX. Dissertation Title: Improved Bioavailability and Site Specific Delivery of Poorly Water Soluble Drugs through the Production of Stabilized Drug Nanoparticles.

19. Jason T. McConville, Ph.D. – (2003-2006; Post-doctoral Research Fellow) – Assistant Professor of Pharmaceutics, University of Texas at Austin, Austin, TX.

20. Prapasri Sinswat, Ph.D. (August, 2006) – Assistant Professor of Pharmaceutics, Chulalongkorn University, Bangkok, Thailand. Dissertation Title: Enhancing the Delivery of Poorly Water Soluble Drugs Using Particle Engineering Technologies.

21. Kirk A. Overhoff, Ph.D. (August, 2006) – Senior Pharmaceutical Scientist, Schering Corporation, Kenilworth, NJ. Dissertation Title: Improved Oral Bioavailability of Poorly Water Soluble Drugs Using Rapid Freezing Processes.

22. Josh D. Engstrom, Ph.D. (August, 2007) – Senior Pharmaceutical Scientist, Bristol Meyers Squibb, Princeton, NJ. Dissertation Title: Stable Submicron Protein Particles: Formation, Properties and Pulmonary Applications.

23. Keat Chow, Ph.D. (2007-2008; Post-doctoral Research Fellow).

24. Masao Nagao, M.S. (2007-2008; Visiting Research Scholar; Takeda Pharmaceuticals, Japan).

25. Dave A. Miller, Ph.D. (August, 2007) – Senior Pharmaceutical Scientist, Hoffman La Roche, Nutley, NJ. Dissertation Title: Improved Oral Absorption of Poorly Water Soluble Drugs by Advanced Solid Dispersion Systems.

26. Michal P. Matteucci, Ph.D. (August, 2007) – Dissertation Title: Highly Supersaturated Aqueous Solutions by Design of Amorphous Pharmaceutical Nanoparticles.

27. Troy P. Purvis, Ph.D. (August, 2007) – Senior Pharmaceutical Scientist, Azaya Therapeutics, San Antonio, TX. Dissertation Title: Nanoparticle Formulations of Poorly Water Soluble Drugs and their Action In Vivo and In Vitro.

28. Yosuhiro Tsutsumi, Ph.D. (2008-2009; Visiting Research Scholar; Daiichi Sankyo Co., Ltd., Pharmaceutical Technology, Japan).

29. Rui Jia, Ph. D. (2008-2009); Visiting Research Scholar; China.

30. Justin A. Tolman, Pharm.D., Ph.D. (January, 2009) – Assistant Professor of Pharmaceutics, School of Pharmacy and Health Professions, Creighton University, Omaha, Nebraska. Dissertation Title: Pulmonary Delivery of Aqueous Voriconazole Solution.

31. Alan B. Watts, Ph.D (July 2009) – Senior Scientist, Microdose Inc., Princeton, NJ, Dissertation Title: Pulmonary Delivery of Tacrolimus for Lung Transplant and Asthma Therapy.

32. Wei Yang, Ph.D. (July 2009) – Senior Scientist, Enavail, LLC, Austin, TX, Dissertation Title: Improvement of Bioavailability of Poorly Water-Soluble Drug via Pulmonary Delivery of Nanoparticles.

33. James C. DiNunzio (July 2009) – Senior Scientist, PharmaForm LLC, Austin, TX, Dissertation Title: Formulation and Processing Technologies for Enhanced Oral Bioavailability of Poorly Water Soluble Compounds.

34. Ikumasa Ohno, Ph.D. (2010-2010; Visiting Research Scholar, Daiichi Sankyo Co., Ltd., Pharmaceutical Technology, Japan).

XII. Publications

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131. Delivery of Poorly Water Soluble Drugs Using Nebulization, Proceedings of the15th Drug Delivery to the Lungs Conference, Aerosol Society, London, England, December, 2004.
132. Comparison of Commercial Itraconazole to Aerosolized Nanoparticle Itraconazole in a Murine Model for the Prevention of Invasive Pulmonary Aspergillus, Proceedings of Alcalde XIX Southwest Leadership Conference, Austin, Texas, April, 2005.
133. Novel Treatment of Pulmonary Aspergillosis Using Nebulized Itraconazole Nanoparticles in the Murine Model, Proceedings of the Respiratory Drug Delivery – Europe 2005 Conference, Paris, France, May, 2005.
134. Improved Dissolution Rate and Bioavailability Through the Formation of a Highly Miscible Binary Mixture, Proceedings of the Controlled Release Society Annual Meeting, Miami, FL, June, 2005.
    a. Paper awarded the Controlled Release Society's Innovative Aspects of Oral Drug Delivery and Absorption Graduate/Post-Doc Award
135. Rapid Release, High Potency Itraconazole Formed by Evaporative Precipitation Into Aqueous Solution, Proceedings of the Controlled Release Society Annual Meeting, Miami, FL, June, 2005.

a. Paper nominated for the Controlled Release Society's Innovative Aspects of Oral Drug Delivery and Absorption Graduate/Post-Doc Award

136. Particle Engineering for Rapid Dissolution Rates of Poorly Water Soluble Drugs, Proceedings of the American Institute of Chemical Engineers 2005 Annual Meeting, Cincinnati, OH, October, 2005.
137. Cryogenic Liquids, Nanoparticles and Microencapsulation, Proceedings of the 15th Symposium on Microencapsulation, Parma, Italy, September, 2005.
    a. Invited Speaker
138. Improved Danazol Supersaturation and Oral Bioavailability via Formulation into an Amorphous Solid Solution, Proceedings of the American Association of Pharmaceutical Scientists Meeting, Nashville, TN, November, 2005.
139. Characterization of Nebulized Itraconazole Nanoparticles and Delivery to the Murine Lung, Proceedings of the American Association of Pharmaceutical Scientists Meeting, Nashville, TN, November, 2005.
140. Treatment of Acute Pulmonary Aspergillosis with Nebulized Itraconazole in the Murine Model, Proceedings of the American Association of Pharmaceutical Scientists Meeting, Nashville, TN, November, 2005.
141. Poorly Water Soluble Drug Nanoparticles by Anitsolvent Precipitation: Mixing Energy Versus Surfactant Stabilization, Proceedings of the American Association of Pharmaceutical Scientists Meeting, Nashville, TN, November, 2005.
142. On-Line Turbidimetric Dissolution Rates of Poorly Water Soluble Drug Nano-structured Particles, Proceedings of the American Association of Pharmaceutical Scientists Meeting, Nashville, TN, November, 2005.
143. Improvement of Dissolution Rate of Repaglinide Using Controlled Precipitation, Proceedings of the American Association of Pharmaceutical Scientists Meeting, Nashville, TN, November, 2005.
144. Novel Processes for the Enteric Coating of Empty Gelatin Capsules, Proceedings of the American Association of Pharmaceutical Scientists Meeting, Nashville, TN, November, 2005.
145. Rapid Dissolving Repaglinide Powders Produced by Ultra-Rapid Freezing Process, Proceedings of the American Association of Pharmaceutical Scientists Meeting, Nashville, TN, November, 2005.
146. Investigation of Dissolution Properties of Microcrystalline or Stabilized Amorphous Particles of Itraconazole in Melt Extruded Solid Dispersions, Proceedings of the American Association of Pharmaceutical Scientists Meeting, Nashville, TN, November, 2005.
147. In vivo Efficacy of Aerosolized Nano-structured Itraconazole Formulations for the Prevention of Invasive Pulmonary Aspergillosis, Proceedings of the 45th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, D.C., December 2005.
148. Murine Airway Histology and Alveolar Macrophage Uptake of Inhaled Amorphous Itraconazole, Proceedings of the American Thoracic Society Meeting, San Diego, CA, May, 2006.
149. Particle Engineering and Formulation for Enhanced Bioavailability of Poorly Water Soluble Drugs, Proceedings of Particles 2006, Medical/Biochemical Diagnostic,

Pharmaceutical and Drug Delivery Applications of Particle Technology, Orlando, FL, May 2006.

150. Single Dose Variability and Multi-Dose Studies of Nebulized Itraconazole in a Murine Model, Proceedings of Respiratory Drug Delivery X, Boca Raton, FL, April 2006.
151. Poorly Water Soluble Drug Nanoparticles by Anitsolvent Precipitation: Mixing Energy Versus Surfactant Stabilization, Proceedings of the Controlled Release Society Meeting, Vienna, Austria, July 2006.
152. Sustained Lung Concentrations of Itraconazole Using Nebulized Dispersions in a Murine Model, Proceedings of the Controlled Release Society Meeting, Vienna, Austria, July 2006.
153. Evaluation of the USP Enteric Test Method A for Delayed-Release Dosage Forms Using PLIF, Proceedings of the Controlled Release Society Meeting, Vienna, Austria, July 2006.
154. Evaluation of the USP Dissolution Test Method A for Enteric Coated Articles by Planer Laser Induced Fluorescence, Proceedings of the World Congress of Pharmacy and Pharmaceutical Sciences 2006, 66th International Congress of FIP, Salvatore, Brazil, August 2006.
155. Aerosolized Itraconazole (ITZ) as Prophylaxis Against Invasive Pulmonary Aspergillosis (IPA) Due to *Aspergillus fumigatus*, Proceedings of the Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, September, 2006.
156. Aerosolized Itraconazole as Prophylaxis Against Invasive Pulmonary Aspergillosis Due to Aspergillus Fumigatus, Proceedings of the American College of Clinical Pharmacy, St. Louis, MO, October, 2006.
157. In-vitro and In-vivo Comparison of Melt Extruded Particulate Dispersions of PVP and HPMC-Stabilized Nano-Structured Amorphous Particles of Itraconazole, Proceedings of the American Association of Pharmaceutical Scientists, San Antonio, TX, October 2006.
158. Formation of Stable Submicron Protein Particles by Thin Film Freezing, Proceedings of the American Association of Pharmaceutical Scientists, San Antonio, TX, October 2006.
159. Anti-solvent Precipitation of Cyclosporin A Nanoparticles for Enhanced Pulmonary Delivery, Proceedings of the American Association of Pharmaceutical Scientists, San Antonio, TX, October 2006.
160. In-vitro and In-vivo Validation of a High Concentration Preclinical Rodent Dosing Apparatus for Inhalation, Proceedings of the American Association of Pharmaceutical Scientists, San Antonio, TX, October 2006.
161. Development of a Modified Release System Containing Itraconazole Using the Ultra-Rapid Freezing Technology, Proceedings of the American Association of Pharmaceutical Scientists, San Antonio, TX, October 2006.
162. Stable Supersaturated Solutions from Nanoparticle Dissolution, Proceedings of the American Association of Pharmaceutical Scientists, San Antonio, TX, October 2006.
163. Evaluation of the USP Dissolution Test Method A for Enteric-Coated Articles by Planar Laser Induced Fluorescence, Proceedings of the American Association of Pharmaceutical Scientists, San Antonio, TX, October 2006.

164. Optimization of Rapidly Disintegrating and Dissolving Tablets Containing Itraconazole Nanoparticles Formed by Evaporative Precipitation Into Aqueous Solution, Proceedings of the American Association of Pharmaceutical Scientists, San Antonio, TX, October 2006.
165. Immunological Response and Alveolar Macrophage Uptake of Inhaled Amorphous ITZ, Proceedings of the American Association of Pharmaceutical Scientists, San Antonio, TX, October 2006.
166. Engineered Particles for Targeted Drug Delivery, Proceedings 15th International Symposium on Microencapsulation, Lexington, Kentucky, September 2007.
167. In Vitro Efficacy and In Vivo Safety of Inhaled Nanoparticles of Tacrolimus, Proceedings of the American College of Chest Physicians, Chicago, IL, October, 2007.
168. Effect of Stabilizer on the Maximum Degree and Extent of Supersaturation and Oral Absorption of Tacrolimus Nanoparticles Made by Ultra-rapid Freezing, Proceedings of the American Association of Pharmaceutical Scientists, San Diego, CA, November, 2007.
169. Improved Bioavailability of Itraconazole via Pulmonary Administration of Nanoparticles Produced by Ultra-rapid Freezing, Proceedings of the American Association of Pharmaceutical Scientists, San Diego, CA, November, 2007.
170. Preformulation and Formulation Studies of Rapidly Dissolving Powders of Sirolimus Produced by the Ultra-Rapid Freezing Process, Proceedings of the American Association of Pharmaceutical Scientists, San Diego, CA, November, 2007.
171. Multiple Dose Pharmacokinetic Study of Tacrolimus Nanoparticles Delivered by Nebulization to Mice, Proceedings of the American Association of Pharmaceutical Scientists, San Diego, CA, November, 2007.
172. The Influence of Hydrophilic and Enteric Polymers in Targeting *In Vitro* Supersaturation of Itraconazole from Engineered Particles, Proceedings of the American Association of Pharmaceutical Scientists, San Diego, CA, November, 2007.
173. Influence of Cyclodextrin on Viscosity and Aerosolization by Nebulization, Proceedings of the American Association of Pharmaceutical Scientists, San Diego, CA, November, 2007.
174. Amphotericin B Formulation Containing Insoluble Aggregates Dispersed in a Lyoprotectant Carrier for Pulmonary Delivery, Proceedings of the American Association of Pharmaceutical Scientists, San Diego, CA, November, 2007.
175. Supersaturation of Itraconazole in Neutral pH from Engineered Particles and Enteric Dispersions of Engineered Particles Produced by Hot-Melt Extrusion, Proceedings of the American Association of Pharmaceutical Scientists, San Diego, CA, November, 2007.
176. Design of Pharmaceutical Nanoparticles for Enhanced Therapies, Proceedings of the American Institute of Chemical Engineering Meeting, Salt Lake City, UT, November, 2007.
177. Suspension of Protein and Poorly Water Soluble Drug Particles for High Dosages with Pressurized Metered Dose Inhalers, Proceedings of the Respiratory Drug Delivery Conference, Scottsdale, AZ, May, 2008.
178. K. P. Johnston, J. Engstrom, J. Tam, M. Matteucci, A. Mazuski, L. Ma, Robert O. Williams III, T. Milner and M. Feldman, Design of Pharmaceutical Nanoparticles for Drug Delivery, Proceedings of the National American Chemical Society Meeting, Philadelphia, PA, August, 2008.

179. A. R. Saad, A. Cline, A. B. Watts, G. Hsiung, J. I. Peters, L. Angel, R. O. Williams III and S. B. Johnson, Nanoparticle Tacrolimus Inhalation in Rat Lung Transplant Model, Proceedings of the American College of Chest Physicians, Philadelphia, PA, October, 2008.
180. J. A. Tolman, N. P. Wiederhold, J. T. McConville, L. K. Najvar, J. R. Graybill, J. J. Coalson, R. Bocanegra, T. F. Patterson and R. O. Williams III, Aerosolized Voriconazole (VRC) as Prophylaxis Against Invasive Pulmonary Aspergillosis (IPA) due to *Aspergillus fumigatus*, Proceedings of the Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington D.C., October 2008.
181. M. A. Mazuski, M. E. Matteucci, R. O. Williams III and K. P. Johnston, Flocculated Amorphous Nanoparticles for Enhanced Bioavailability of Poorly-Water Soluble Drugs: In Vitro and In Vivo Studies, American Institute of Chemical Engineering, Philadelphia, PA, November 2008.
182. J. D. Engstrom, J. Tam, M. A. Mazuski, R. O. Williams III and K. P. Johnston, Stable Suspensions of Protein and Poorly Water Soluble Drug Particles for High Dosages with Pressurized Metered Dose Inhalers, American Institute of Chemical Engineering, Philadelphia, PA, November 2008.
183. N. A. Nelson, N. P. Wiederhold, R. O. Williams III and Cr. R. Frei, Incidence and Clinical Relevance of Viral Co-infection Among Patients with Invasive Aspergillosis (IA) in the United States, 48th Annual ICAAC/IDSA 46th Annual Meeting, Washington, DC, October, 2008.
184. S. Bosselmann, R. O. Williams III, N. P. Wiederhold and C. R. Frei, Regional and Seasonal Variations in Invasive Aspergillosis in the United States over the Last Decade, 48th Annual ICAAC/IDSA 46th Annual Meeting, Washington, DC, October, 2008.
185. W. Yang, K. P. Johnston and R. O. Williams III, Comparison of Bioavailability of Amorphous Versus Crystalline Nanoparticulate Itraconazole Via Pulmonary Administration in Rats, Proceedings of the American Association of Pharmaceutical Scientists, Atlanta, GA, November 2008.
186. J. DiNunzio, C. Brough, R. O. Williams III and J. W. McGinity, Production of Plasticizer Free Itraconazole Solid Dispersions for Enhanced Solid State Properties Using KinetiSol Dispersion, Proceedings of the American Association of Pharmaceutical Scientists, Atlanta, GA, November 2008.
187. J. DiNunzio, C. Brough, A. Brown, R. O. Williams III and J. W. McGinity, Fusion Processing of Itraconazole and Griseofulvin Solid Dispersions by a Novel High Energy Manufacturing Technology – KinetiSol Dispersing, Proceedings of the American Association of Pharmaceutical Scientists, Atlanta, GA, November 2008.
188. Y. Tsutsumi, K. T. Chow, W. Yang and R. O. Williams III, Preparation and Characterization of Solid Dispersions of Itraconazole and Enteric Polymers Made by Spray Freezing into Liquid Technology, Proceedings of the American Association of Pharmaceutical Scientists, Atlanta, GA, November 2008.
189. K. O'Donnell, R. O. Williams III, C. Wah and J. T. McConville, Investigation of Nebulized Dose and Inhaled Dose of Itraconazole Dispersions in a Nose Only Rodent Dosing Chamber, Proceedings of the American Association of Pharmaceutical Scientists, Atlanta, GA, November 2008.
190. J. Tam, J. Engstrom, M. Mazuski, R. O. Williams III, and K. P. Johnston, Stable Suspensions of Protein and Poorly Water Soluble Drug Particles for High Dosages with

Pressurized Metered Dose Inhalers, Proceedings of the American Association of Pharmaceutical Scientists, Atlanta, GA, November 2008.

191. A. B. Watts, A. Saad, A. Cline, G. Hsiung, S. Johnson, J. I. Peters and Robert O. Williams III, Pulmonary Administration of a Novel Amorphous Tacrolimus Formulation in a Lung Transplanted Rat Model, Proceedings of the American Association of Pharmaceutical Scientists, Atlanta, GA, November 2008.
192. K. T. Chow, W. Yang and R. O. Williams III, Dissolution Enhancement of Itraconazole Prepared by a Modified Spray Freezing into Liquid Process with Template Emulsion, Proceedings of the American Association of Pharmaceutical Scientists, Atlanta, GA, November 2008.
193. M. Nagao, S. Bosselmann and R. O. Williams III, Preparation of Itraconazole Nanoparticles by Advanced Evaporative Precipitation into Aqueous Solution, Proceedings of the American Association of Pharmaceutical Scientists, Atlanta, GA, November 2008.
194. J. Tolman, N. Nelson, S. Bosselmann, N. Wiederhold and R. O. Williams III, Pharmacokinetic Profile Following Multiple Doses of Inhaled Voriconazole Solution in Mice, Proceedings of the American Association of Pharmaceutical Scientists, Atlanta, GA, November 2008.
195. J. Tolman, Y. Son, N. Wiederhold, J. T. McConville and R. O. Williams III, Aerosol Characterization and Single Dose Pharmacokinetic Analysis of Nebulized Voriconazole Solution, Proceedings of the American Association of Pharmaceutical Scientists, Atlanta, GA, November 2008.
196. J. C. DiNunzio, C. Brough, R. O. Williams III and J. W. McGinity, In Vitro Characterization of Concentration Enhancing Polymer Solid Dispersions Containing Itraconazole Produced by KinetiSol Dispersing, Proceedings of the Controlled Release Society, Copenhagen, Denmark, July, 2009.
197. Y. Tsutsumi, J. C. DiNunzio, K. T. Chow, W. Yang and R. O. Williams III, Preparation and Characterization of Solid Dispersions of Itraconazole and Enteric Polymers Made by Spray Freezing Into Liquid Technology, Proceedings of the 17th International Society of Microencapsulation, Nagoya, Japan, September, 2009.
198. S. Bosselmann, D. Owens, M. Herpin, R. Kennedy and R. O. Williams III, Enhanced Stability of Itraconazole Hot-Melt Extrudates Through the Deposition of a Hydrophobic Plasma-Polymerized Film, Proceedings of the American Association of Pharmaceutical Scientists, Los Angeles, CA, November 2009.
199. K. O'Donnell, R. O. Williams III, H. Lirola and J. T. McConville, Investigation of Nebulized Itraconazole Dispersions: In-Vitro-In-Vivo Comparison of Dose Administered to Mice in a Nose-only Dosing Apparatus, Proceedings of the American Association of Pharmaceutical Scientists, Los Angeles, CA, November 2009.
200. A. Watts, Y. Son, J. T. McConville and R. O. Williams III, Nanostructured Tacrolimus Produced by Ultra-rapid Freezing for Dry Powder Inhalation, Proceedings of the American Association of Pharmaceutical Scientists, Los Angeles, CA, November 2009.
201. W. Yang, K. Chow, B. Lang, K. P. Johnston and R. O. Williams III, Pharmacokinetic Study of Inhaled Nebulized Itraconazole as Cyclodextrin Solubilized Solution or Colloidal Dispersion in Mice, Proceedings of the American Association of Pharmaceutical Scientists, Los Angeles, CA, November 2009.

202. K. Chow, W. Yang, Y. Tsutsumi and R. O. Williams III, Particle Engineering Studies for Solubility Enhancement of Itraconazole Using Fine Emusion Templating and Cosolvent Approaches with Ultra-rapid Freezing, Proceedings of the American Association of Pharmaceutical Scientists, Los Angeles, CA, November 2009.
203. J. DiNunzio, C. Brough, J. Hughey, R. O. Williams III and J. W. McGinity, Solid Dispersion Production Containing a Temperature Sensitive Drug via Hote Melt Extrusion and KinetiSol Dispersing, Proceedings of the American Association of Pharmaceutical Scientists, Los Angeles, CA, November 2009.
204. S. Bosselmann,, D. E. Owens III, R. L. Kennedy, M. J. Herpin and R. O. Williams III, Enhanced Stability of Amorphous Ketoprofen Made by Rapid Freezing Through the Deposition of Hydrophobic Plasma-Polymerized Films, Proceedings of Particles 2010: Medical/Biochemical Diagnostic, Pharmaceutical and Drug Delivery Applications of Particle Technology, Orlando, FL, May, 2010.
205. S. Bosselmann, M. Nagao, K. T. Chow and R. O. Williams III, Formulation and Characterization of Itraconazole Nanoparticles Made by Advanced Evaporative Precipitation Into Aqueous Solution, Proceedings of Particles 2010: Medical/Biochemical Diagnostic, Pharmaceutical and Drug Delivery Applications of Particle Technology, Orlando, FL, May, 2010. (Invited)
206. B. Windsor, D. E. Owens III, W. Yang, A. B. Watts and R. O. Williams III, Benefits of Nanostructured Compositions Made by Rapid Freezing to Drug Delivery, Proceedings of Particles 2010: Medical/Biochemical Diagnostic, Pharmaceutical and Drug Delivery Applications of Particle Technology, Orlando, FL, May, 2010. (Invited)
207. W. Yang and R. O. Williams III, Comparison of Bioavailability of Engineered Amorphous Nanoparticles Versus Crystalline Nanoparticles and Cyclodextrin Encapsulated Itraconazole Compositions via Pulmonary Administration in Rodents, Proceedings of the Respiratory Drug Delivery Conference, Orlando, FL, April, 2010. (Invited)
208. S. Bosselmann, D. E. Owens III, R. L. Kennedy, M. J. Herpin and R. O. Williams III, Novel Plasma Deposited Stability Enhancement Coating for Amorphous Ketoprofen, Proceedings of the 240th American Chemical Society Meeting (Polymeric Materials: Science and Engineering), Boston, MA, August, 2010. (Invited)
209. K. P. O'Donnell, P. Schmerler and R. O. Williams III, Investigation of a Novel Solvent Removal Technique, Atmospheric Freeze Drying, on the Physico-chemical Properties of Pharmaceutical Powders, Proceedings of the American Association of Pharmaceutical Scientists, New Orleans, LA, November 2010.
210. W. Yang, D. Owens, B. Lang and R. O. Williams III, Production and Characterization of Nano-structured Beclomethasone Dipropionate Powders Prepared by Rapid Freezing for Dry Powder Inhalation, Proceedings of the American Association of Pharmaceutical Scientists, New Orleans, LA, November 2010.
211. N. Beinborn, H. Lirola and R. O. Williams III, Effect of Process Variables on Morphology of Voriconazole Formulations Produced by Thin Film Freezing, Proceedings of the American Association of Pharmaceutical Scientists, New Orleans, LA, November 2010.
212. H. Li, M. Zhang, B. Lang, K. P. O'Donnell and R. O. Williams III, Modified Release Carbamazepine Compositions Prepared by Thin Film Freezing, Proceedings of the American Association of Pharmaceutical Scientists, New Orleans, LA, November 2010.

213. R. Bennett, J. Hughey, C. Brough, R. O. Williams III and J. W. McGinity, Solid Dispersion Comparisons of Griseofulvin in Eudragit L100-55 Carrier Processed by Hot Melt Extrusion and KinetiSol Dispersing, Proceedings of the American Association of Pharmaceutical Scientists, New Orleans, LA, November 2010.
214. J. Hughey, J. DiNunzio, R. Bennett, C. Brough, D. Miller, H. Ma, R. O. Williams III and J. W. McGinity, The Preparation of Enteric Solid Dispersions of a Chemically Unstable BCS Class II Compound by Hot Melt Extrusion and KinetiSol Dispersing, Proceedings of the American Association of Pharmaceutical Scientists, New Orleans, LA, November 2010.
215. B. Lang and R. O. Williams III, Influence of Excipient Type on Itraconazole Compositions Made by Thin Film Freezing-Emulsion Process, Proceedings of the American Association of Pharmaceutical Scientists, New Orleans, LA, November 2010.
216. B. Lang and R. O. Williams III, Engineered Itraconazole Compositions by Thin Film Freezing: Emulsion vs. Cosolvent Solution Process, Proceedings of the American Association of Pharmaceutical Scientists, New Orleans, LA, November 2010.
217. M. Zhang, H. Li, B. Lang, K. O'Donnell, C. Wu and R. O. Williams III, Amorphous Compositions of Fenofibrate Prepared by Thin Film Freezing, Proceedings of the American Association of Pharmaceutical Scientists, New Orleans, LA, November 2010.
218. S. Bosselmann, K. Chow, M. Nagao and R. O. Williams III, Enhanced Dissolution of Amorphous Itraconazole Nanoparticles Produced by Advanced Evaporative Precipitation into Aqueous Solution, Proceedings of the American Association of Pharmaceutical Scientists, New Orleans, LA, November 2010.

XIV. Invited Talks

1. Proprietes de Compaction de Poudres, Servier Laboratories, Orleans, France, June, 1985.

2. A Study of the Influence of Magnesium Stearate or Talc on the Compaction Properties of Aspirin and Sodium Sulfathiazole Using Tableting Indices, Proceedings of the Fourth International Conference on Pharmaceutical Technology, Paris, France, June, 1986.

3. Tableting - An Industrial Viewpoint, Pharmaceutics Series, University of Cincinnati, Cincinnati, OH, October, 1990.

4. Utilization of Sodium Chloride, Fructose, and Urea to Modify the Surface Tension of RG-12915A Solutions, The University of Texas at Austin, Austin, TX, September, 1991.

5. Tableting Indices in Compaction Studies, Proc. Midwest Regional Meeting, American Association of Pharmaceutical Scientists, Chicago, IL, May, 1992.

6. Theory and Practical Applications of Tableting Indices in Compaction Studies, Proc. Fifth Annual Meeting, Proceedings of the American Association of Pharmaceutical Scientists, Las Vegas, NV, November, 1990.
    a. Invited Speaker

7. Current Issues and Trends in Technology Transfer, Sixth International Congress for Pharmaceutical Engineering, International Society for Pharmaceutical Engineering, Philadelphia, PA, May, 1994.
    a. Invited Speaker

8. Simulated Food Effects on Drug Release from Film Coated Pellets, Proceedings of the 15th Pharmaceutical Technology Conference, Oxford, England, March, 1996.

9. Optimization of Metered-Dose Inhaler Suspension Formulations, Fachbereich Pharmazie, Freie Universitat Berlin, Berlin, Germany, March, 1996.

10. Formulation and Stability of a Three Component Suspension, Horizon Pharmaceuticals, Louisville, KY, May, 1996.

11. Optimization of a Matrix Tablet Formulation Containing Nonoxynol-9 Using Cellulose Ethers, The Dow Chemical Company, Cellulosics Division, Midland, MI, November, 1997.

12. Delivering Steroids to the Nose Using an Aqueous Based Pump System, Honduran Medical Association, Tegucigalpa, Honduras, Central America, October, 1998.
    a. Invited Plenary Speaker

13. Preparation of Chitosan Microspheres for Nasal and Pulmonary Release of Therapeutic Macromolecules, Proceedings of the Association of Pharmaceutical Technology Professors of Spain, Santiago, Spain, February, 1999.

14. The Effect of Co-Grinding Drug and a Polymeric Surfactant on a Model pMDI Suspension, Proceedings of the 18th Pharmaceutical Technology Conference, Utrecht, The Netherlands, April, 1999.
    a. Invited Speaker

15. Buccal Delivery of Insulin Via Aerosol Spray, Proceedings of the Third World Meeting On Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Berlin, Germany, April, 2000.
    a. Session Chair – Scientific Program

16. Introduction to Pharmaceutical Development and Technology, Invited Short Course, International Society of Pharmaceutical Engineers, Philadelphia, PA, May, 2001.
    a. Invited Speaker

17. Utilization of a Novel Cryogenic Spray-freezing Into Liquid (SFL) Process to Encapsulate Danazol, Proceedings of the 13th International Symposium on Microencapsulation, Angers, France, September, 2001.
    a. Session Chair – Scientific Program

18. Austin's Road to Bio: Where We Are and Where We're Going – Drug Delivery and Nanotechnology. Austin Chamber of Commerce, Austin, TX, January, 2003.
    a. Invited Expert Panel – Speaker

19. Improvement of Dissolution Rates of Poorly Water Soluble Drugs Using A New Particle Engineering Technology – Spray Freezing into Liquid. Proceedings of the American Chemical Society, Polymeric Drug Delivery: Science and Application, New York, NY, September, 2003.
    a. Invited Speaker
    b. Session Chair – Engineered Drug Particles

20. Enabling Technologies Helping to Expand Drug Delivery in the Pharmaceutical Industry: Nanotechnology. International Conference on Drug Development, Austin, Texas, February, 2004.
    a. Invited Speaker

21. Novel Processes to Enhance Dissolution and Bioavailability of Poorly Water Soluble Drugs, Barnett International Conference on Strategies for Improving Solubility, Philadelphia, PA, June 2004.
    a. Invited Speaker

22. Recent Advances in Particle Engineering Processes – Precipitation and Freezing, Short Course, Advances in Controlled Release and Drug Delivery Technologies, The Center for Microencapsulation & Drug Delivery, College Station, TX, October 2004.
    a. Invited Speaker

23. Solid Dispersions and Nanotechnology Systems for Poorly Water Soluble Drugs, Second Annual Anthony P. Simonelli Conference in Pharmaceutical Sciences, Long Island University, New York, NY, June, 2005.
    a. Invited Speaker

24. Cryogenic Liquids, Nanoparticles and Microencapsulation, 15th International Symposium on Microencapsulation, Parma, Italy, September 2005.
    a. Invited Lecture

25. Nanoparticles for Pharmaceutical Applications, DPT Laboratories, LTD., San Antonio, TX, October 2005.
    a. Invited Lecture

26. Texas Life Sciences: More Than Just Your Medicine Cabinet, Proceedings of the Bio Texas Summit 06 Meeting, Austin, TX, February, 2006.
    a. Invited Lecture and Panelist

27. Enabling Technologies Helping to Expand Drug Delivery in the Pharmaceutical Industry: Nanotechnology, Committee of Emerging Technology and Telecommunications, City of Austin, Austin, TX, July 2006.
    a. Invited Lecture

28. Manufacturing Challenges for Production of Nanoparticles. Proceedings of the World Congress of Pharmacy and Pharmaceutical Sciences 2006, 66th International Congress of FIP, Salvatore, Brazil, August 2006.
    a. Invited Lecture

29. An Alternative Route of Delivery for Antifungal Drugs to Treat Fungal Infections – Pulmonary Drug Delivery. Asuragen Inc., Austin, TX, January 2007.
    a. Invited Lecture

30. Positioning Investors for the Nest Wave in Pain Management, Fentanyl Taifun – Inhaled Fentanyl for Breakthrough Pain, Oppenheimer Healthcare, New York City, NY, March, 2007.
    a. Invited Lecture

31. Advances in Pulmonary Drug Delivery – Inhaled Nanoparticles, Distinguished Faculty Seminar, Celebrating Research Achievements, University of Texas at Austin, College of Pharmacy, Austin, Texas, April, 2007.
    a. Invited Lecture

32. Pharmaceutical Development in a Collaborative Setting: A Successful Formula, Proceedings of the International Biotechnology Congress and Exhibition: BioMonterrey 08, Monterrey, Mexico, October 2008.
    a. Invited Lecture
33. Pulmonary Delivery of Itraconazole Nanoparticles to Treat Life Threatening Fungal Infections, School of Pharmacy, University of Kansas, Lawrence, KS, April 2009.
    a. Invited Lecture
34. Formulation and Characterization of Itraconazole Nanoparticles Made by Advanced Evaporative Precipitation Into Aqueous Solution, Proceedings of Particles 2010, Orlando, FL, May, 2010.
    a. Invited Lecture
35. Novel Plasma Deposited Stability Enhancement Coating for Amorphous Ketoprofen, Proceedings of the 240th American Chemical Society Meeting (Polymeric Materials: Science and Engineering), Boston, MA, August, 2010.
    a. Invited Lecture – Stephanie Bosselmann
36. Novel Particle Engineering Technologies for Enhancing Bioavailability, February, 2010
    a. Merck & Company, Kenilworth, NJ
    b. Hoffmann LaRoche, Nutley, NJ
    c. Columbia Laboratories, Inc., Livingston, NJ
    d. ThePharmaNetwork, West Orange, NJ

XV. Book Reviews

1. R. O. Williams III. Solubility and Solubilization in Aqueous Media. By Samuel H. Yalkowsky (University of Arizona). Oxford University Press: New York. 1999. xvi + 464 pp., J. Am. Chem. Soc. (2000), 122(40) 9882.

XVI. Invited Book Chapters and Books

1. V. Mahaguna, R. O. Williams III and T. C. Hardin, Trends in Antifungal Research. In P. Jolles (ed.), *New Approaches to Drug Development*, Birkhauser Publishers, Boston, (2000) 55-68.

2. R. O. Williams III and V. Mahaguna, Coatings. In A. Gennar (ed.), *FMC Problem Solver and Reference Manual*, Published by FMC Corporation, Princeton, 2000.

3. J. M. Vaughn and R. O. Williams III, Pharmaceutical Calculations and Compounding. In D. Ginsberg (ed.), *ASHP's PharmPrep, Second Edition*. Published by the American Society of Health-System Pharmacists, Bethesda, MD, 2003.

4. K. A. Overhoff, K. P. Johnston and R. O. Williams III, Improvement of Dissolution Rate of Poorly Water Soluble Drugs Using a New Particle Engineering Process – Spray Freezing Into Liquid. In S. Svenson (ed.), *Polymeric Drug Delivery Volume II – Polymeric Matrices and Drug Particle Engineering*, Published by ACS Symposium Series, Vol. 924, American Chemical Society, Washington, D.C., 2005.

5. K. A. Overhoff, A. Moreno, D. A. Miller, K. P. Johnston and R. O. Williams III, Advances in Drug Delivery Technologies for Nanoparticulates. In J. Zach Hilt, J. Brock Thomas and N. A. Peppas (eds.), *Nanotechnology in Therapeutics: Current Technology and Applications*, Published by Horizon Scientific Press, Norwich, United Kingdom, 2007.

6. J. M. Vaughn, K. R. Vaughn and R. O. Williams III, Pharmaceutical Calculations and Compounding. In D. Ginsberg (ed.), *ASHP's PharmPrep, Third Edition*. Bethesda: American Society of Health-System Pharmacists, Bethesda, 2007. Online version: updated annually, 2007, 2008, 2009. www.pharmpreponline.com.

7. J. M. Vaughn, K. P. O'Donnell and R. O. Williams III, Pharmaceutical Calculations and Compounding. In D. Ginsberg (ed.), *ASHP's PharmPrep, Fourth Edition*. Bethesda: American Society of Health-System Pharmacists, Bethesda. Online version: updated 2010. www.pharmpreponline.com.

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ABBOTT LABORATORIES and ABBOTT RESPIRATORY LLC Plaintiffs, v. TEVA PHARMACEUTICAL INDUSTRIES, LTD. and TEVA PHARMACEUTICALS USA, INC., Defendants.	C.A. No. 10-57 (SLR)(MPT) CONSOLIDATED
ABBOTT LABORATORIES and ABBOTT RESPIRATORY LLC Plaintiffs, v. WATSON LABORATORIES, INC. - FLORIDA, Defendant.	

DECLARATION OF MICHAEL B. BOTTORFF IN SUPPORT OF PLAINTIFFS' OPENING CLAIM CONSTRUCTION BRIEF

I, Michael B. Bottorff, Pharm.D., submit this declaration in support of the Opening Claim Construction Brief of Plaintiffs Abbott Laboratories and Abbott Respiratory LLC (collectively, "Abbott").

I. INTRODUCTION

1. I have been retained by Abbott to provide expert opinions and testimony in the above-captioned case. I understand that Abbott has filed suit against Teva Pharmaceuticals

USA, Inc. and Teva Pharmaceutical Industries, Ltd. (collectively, "Teva") and Watson Laboratories, Inc.-Florida ("Watson") (collectively "Defendants") and has alleged that Defendants' filing of certain Abbreviated New Drug Applications ("ANDAs") for the approval of generic versions of Abbott's drug SIMCOR® infringes certain identified claims of U.S. Patent Nos. 6,080,428 ("the '428 patent"), 6,129,930 ("the '930 patent"), 7,011,848 ("the '848 patent"), 6,818,229 ("the '229 patent"), 6,406,715 ("the '715 patent"), 6,676,967 ("the '967 patent"), and 6,746,691 ("the '691 patent") (collectively, the "SIMCOR® Patents"). I have been asked to provide background on the metabolism of niacin and comment on the meaning of certain terms in the claims of the SIMCOR® Patents from the perspective of one of ordinary skill in the art in the mid-1990s.

A. Background

2. I am a full professor and chair of the Department of Pharmacy Practice in the School of Pharmacy at South College in Knoxville, Tennessee. I joined the faculty at South College in November 2011. One of my primary responsibilities at South College is to start a clinical pharmacy practice that specializes in the treatment of lipid disorders.

3. From 2009 until November 2011, I was a full professor and department chair at the University of Charleston School of Pharmacy, Department of Pharmacy Practice. Through my work at the University of Charleston, I was the co-director of PharmUC, a cardiovascular risk reduction clinic at the University of Charleston School of Pharmacy. Prior to my experience with PharmUC, I spent 20 years at the University of Cincinnati, teaching courses on the therapeutics of cardiology drugs, conducting clinical research, and having a clinical practice with the cardiology department at the University of Cincinnati School of Medicine.

4. My current responsibilities include teaching, conducting clinical research, and overseeing the clinical pharmacy practice at South College. For the past 30 years, I have taught courses on the treatment of cardiovascular diseases, including the clinical pharmacology of antilipidemia therapies, clinical pharmacokinetics, regulatory aspects of drug approval, and pharmacogenomics.

5. My research interests include the study of the metabolism of cardiovascular drugs. During my career, I have been involved in numerous studies involving the pharmacokinetics, bioavailability, metabolism, and drug interactions of cardiovascular drugs. In particular, I was a principal investigator on clinical trials investigating statin metabolism and drug interactions.

6. From 2000 to 2007, I chaired the National Pharmacy Cardiovascular Council. As part of this work, I published a handbook of lipid disorders for pharmacists. I also developed training programs through the National Pharmacy Cardiovascular Council for pharmacists managing their own lipid clinics.

7. I am a fellow of the National Lipid Association and am board-certified by that organization as a lipid specialist. I also serve on the editorial board of the *Journal of Clinical Lipidology*, the journal of the National Lipid Association. I published a comprehensive overview of cholesterol therapies and their drug interactions through the National Lipid Association for use by members of the entire medical community.

8. I have been the author of over 100 peer-reviewed abstracts and articles in the field of clinical pharmacology, pharmacokinetics, and metabolism. Many of these publications have involved the bioavailability and pharmacokinetics of cardiovascular drugs, including antilipidemia drugs, such as statins.

9. In 1976, I received my Bachelor of Science in Industrial Management with honors from the Georgia Institute of Technology. I received my Doctor of Pharmacy in 1981 with high distinction from the University of Kentucky. From 1981 until 1983, I was a pharmacy resident at the Albert B. Chandler Medical Center, University of Kentucky College of Pharmacy. I was chief resident from 1982 until 1983.

10. From 1983 until 1988, I was an Assistant Professor in the Department of Clinical Pharmacy at the University of Tennessee, Memphis. From 1988 until 1989, I was an Associate Professor and Director of Educational Programs at the University of Tennessee, Memphis.

11. From 1989 until 1997, I was an Associate Professor at the University of Cincinnati, Division of Pharmacotherapy. I served as Chairman of the Division of Pharmacotherapy from 1989 until 1994. I became a full professor at the University of Cincinnati College of Pharmacy, Division of Pharmacy Practice in 1997. I remained at the University of Cincinnati College of Pharmacy until 2009, when I was appointed Professor and Chair of Pharmacy Practice at the University of Charleston School of Pharmacy. I left the University of Charleston in November 2011 to take my current position at South College.

12. I am or have been a member of numerous scientific societies, including: the Rho-Chi Honor Society, the American Association of Colleges of Pharmacy (1983-89, 2009-present), the American College of Clinical Pharmacy (1985-present), the American Heart Association (1983-89, 2008-present), the American Society for Clinical Pharmacology and Therapeutics (1985-1999), the American Pharmaceutical Association (1990-93), and the National Lipid Association (2006-present). I have chaired the cardiology section of the American College of Clinical Pharmacy and the clinical practice section of the American Pharmaceutical Association.

13. During my career, I have received numerous honors and awards. For example, I have been elected as a fellow to the National Lipid Association and American College of Clinical Pharmacy.

14. I am or have been a member of editorial boards, including: *Journal of Applied Therapeutic Research* (1997-present); *Pharmacotherapy* (1998-2007); *Cardiology Review* (1991-2000); *Journal of Clinical Lipidology* (2007-present). I currently serve as a referee for numerous peer-reviewed publications in the area of the pharmaceutical sciences and medicine.

15. I have also served as a drug development consultant to various pharmaceutical companies including, for example, Merck and Bristol-Myers Squibb. I have given presentations regarding lipid and cardiovascular therapies as a member of the speakers' bureau for several pharmaceutical companies, including Bristol-Myers Squibb, Astra-Zeneca, Pfizer, Boehringer-Ingelheim, Sanofi-Aventis, Astellas, Merck, and Kos Pharmaceuticals. I have also served as a consultant to several state Medicaid boards, advising them on management of their drug formularies. In addition, I testified before the FDA in 1999 when it considered approving statins for over-the-counter sales.

16. My curriculum vitae is attached as Exhibit A to this declaration.

II. BACKGROUND OF THE INVENTION

A. Dosage Forms of Niacin

17. Prior to 1997, there were two dosage forms of niacin available: immediate release and sustained-release niacin. As a practical matter, however, clinically significant, unpleasant (and sometimes dangerous) side effects arising from the administration of the prior art forms of niacin limited their use in treating cholesterol disorders.

1. "Immediate Release" Niacin

18. Historically, immediate release niacin was the first niacin formulation to be used in the treatment of lipid disorders.

19. In general, the term "immediate release" refers to products that dissolve quickly after ingestion and are formulated with no intent to modify their rate of release.

20. For immediate release formulations of niacin, the niacin is generally released and absorbed into the systemic circulation shortly after oral administration (e.g., about 30 to 60 minutes after the tablet has been ingested).

21. When used to treat dyslipidemia, immediate release niacin was typically administered three times per day in amounts of 1.5 g - 3 g daily. *See, e.g.*, Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults ("ATP I"), at 54-55.

22. The use of immediate release niacin, however, has long been linked to "flushing." Flushing is manifested as redness, warmth, tingling, or itching that occurs on a patient's face, neck, chest, or back. Flushing is an extremely uncomfortable and disturbing side effect of niacin treatment that some patients find unbearable.

23. Almost all patients experience some form of flushing for some period of time after initiating niacin therapy. The extent, frequency, and duration of flushing varies from patient to patient. In my experience, despite its proven effectiveness in treating lipid disorders, many patients stop taking immediate-release niacin because of the flushing side effect.

2. "Sustained-Release" Niacin

24. Sustained-release niacin formulations were developed to avoid or reduce the flushing associated with immediate release niacin.

25. "Sustained-release" refers generally to the release of a drug product's active ingredient over a period of time longer than conventional immediate release formulations.

26. The term "sustained-release" is used interchangeably with other terms, such as "time-released," "controlled-release," and "extended-release." Like "sustained-release," all of those terms refer to formulations in which the rate of release of the active ingredient is slower than the rate of its release from immediate release dosage forms.

27. Prior to the inventions claimed in the SIMCOR® patents, when used to treat dyslipidemia, sustained-release niacin formulations were administered at least twice per day in amounts of 1 g - 2 g per day. *See, e.g.*, Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults ("ATP II"), at III-6.

28. Although sustained-release niacin products were sometimes effective in reducing the flushing associated with therapeutic amounts of immediate release niacin, the use of sustained-release niacin was associated with a much more significant and dangerous side effect: hepatotoxicity (*i.e.*, liver damage).

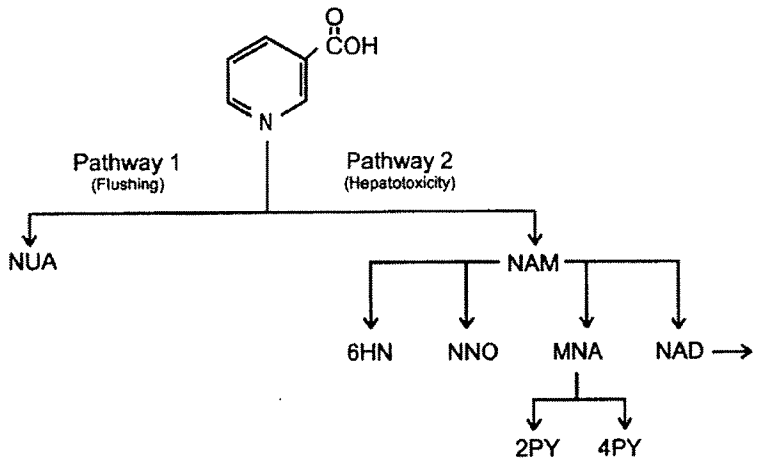
B. The Metabolism of Niacin

29. The side effects associated with both the immediate release and sustained-release forms of niacin can be attributed to niacin's unique metabolism.

30. Niacin, like many drugs that are administered orally, dissolves in the stomach and is preferentially absorbed in the proximal portion of the intestinal tract into the systemic circulation. After it is absorbed, but before it enters the general circulation of the body, it is transported by the portal vein directly to the liver. Upon entering the liver, niacin undergoes first-pass metabolism, *i.e.*, niacin is metabolized prior to entering the general circulation.

31. As illustrated by Figure 2 of the '715 patent, shown below, the liver utilizes two major biochemical pathways for metabolism of niacin. Although it was understood that there

were multiple pathways for the metabolism of niacin, the relationship between those two pathways and the side effects associated with various forms of niacin was not understood prior to the contributions by the inventors of the SIMCOR® patents. The inventors discovered that they could control the amount of niacin metabolized by the respective pathways through manipulating the release rate of niacin. This discovery allowed the inventors to manage the contribution of each pathway in causing the side effects of niacin-based therapies.



'715 Patent, Fig. 2

1. Pathway 2: Hepatotoxicity

32. Although its name may suggest the opposite, Pathway 2 is actually the initial and primary pathway by which the liver metabolizes niacin. Niacin is broken down by Pathway 2 into several different niacin metabolites. One or more of these metabolites may cause hepatotoxicity.

33. Pathway 2 can become "saturated," which means that it may not be able to metabolize all the niacin present in the liver over a short period of time. Saturation occurs when all of the available Pathway 2 enzymes are being used in the niacin metabolism process, leaving no enzymes free to break down any additional unchanged niacin. Thus, Pathway 2 becomes

saturated when the amount of niacin that is transported to the liver is greater than the amount of niacin that the enzymes can break down. When Pathway 2 becomes saturated, the excess niacin "spills over" to a secondary metabolic pathway, which the inventors of the '715 patent called "Pathway 1."

34. In the case of immediate release niacin, a large amount of niacin is transported to the liver rapidly, and Pathway 2 becomes quickly saturated. As a result, Pathway 1 predominates and relatively low amounts of the hepatotoxicity-causing Pathway 2 metabolites are produced.

35. In the case of many sustained-release niacin formulations, after ingestion, the niacin is gradually released into the upper gastrointestinal tract and transported to the liver. Because the niacin is delivered to the liver more slowly than with immediate release niacin, the Pathway 2 enzymes are able to metabolize most or all of the niacin. As a result, greater quantities of the hepatotoxicity-causing Pathway 2 metabolites are produced.

36. The problem is compounded when the sustained-release niacin product is dosed two or more times per day, as was the typical dosing regimen with these products prior to the invention described in the patents-in-suit. When sustained-release niacin is administered multiple times per day, the body will be continuously exposed to a metabolite profile associated with hepatotoxicity.

2. Pathway 1: Flushing

37. "Pathway 1" is the "spill over" pathway associated with niacin. When the enzymes of Pathway 2 become saturated, the excess unchanged niacin will be metabolized by Pathway 1 into nicotinuric acid ("NUA") or appear in the general circulation as unmetabolized niacin. Predominant metabolism of niacin by Pathway 1 is associated with flushing.

38. Immediate release niacin is associated with flushing because it is metabolized primarily by Pathway 1. When immediate release niacin is ingested, all of the niacin will be

rapidly absorbed by the upper gastrointestinal tract and transported to the liver. Pathway 2 will quickly become saturated with niacin, forcing most of the niacin to "spill over" to Pathway 1.

3. Urinary Metabolite Analysis

39. The body clears the metabolites for many drugs (including niacin) through the urine, and the characterization of the urinary metabolites produced by a particular drug following ingestion is an analytical technique for understanding drug metabolism.

40. For niacin, the relative amounts of Pathway 1 and Pathway 2 metabolites produced may be analyzed by measuring the urinary excretion of metabolites from patients following administration of a particular niacin formulation. As discussed above, the release rate of niacin controls the relative amounts of Pathway 1 and Pathway 2 metabolites produced. Therefore, a particular niacin formulation will have a unique urinary metabolite profile (*i.e.*, the ratio of Pathway 1 and Pathway 2 metabolites) that depends upon the release rate of the formulation.

C. The Invention of the '715 Patent

41. The inventors of the '715 patent determined that to avoid or minimize the side effects of immediate release and sustained release niacin, it was necessary to achieve a niacin formulation having a release rate that balances the metabolism of niacin between Pathway 1 and Pathway 2. *See* '715 patent, 14:22-28

42. The '715 patent claims intermediate release niacin formulations with unique ranges of urinary metabolite profiles that balance the metabolism between Pathway 1 and Pathway 2 in a way that minimizes the side effects of niacin.

III. OPINION

A. Ordinary Skill in the Art

43. I understand that for the purposes of construing the disputed claim terms, it is necessary to examine those terms from the viewpoint of a person of ordinary skill in the art at the time of the invention.

44. The arts relevant to the SIMCOR® Patents are the design, formulation, and testing of oral solid dosage forms; biopharmaceutics and pharmacokinetics; and the treatment of patients with lipid disorders.

45. In my opinion, a person of ordinary skill in the art with respect to the SIMCOR® Patents in the early to mid-1990s would have basic knowledge of solid oral dosage formulation, biopharmaceutics and pharmacokinetics, and the treatment of lipid disorders, either through experience working in drug development and formulation or through training (such as a degree in pharmacy or a medical degree), and several years of experience or training in one or more of the relevant arts.

B. Disputed Claim Terms

46. I have been asked to provide my opinion regarding the understanding of a person of ordinary skill in the art in the mid-1990s regarding the terms "in vivo urinary metabolite profile," as used in claim 5 of the '715 patent.[1]

[1] Claims 1 and 9 of the '715 patent refer to an "in vitro urinary metabolite profile." The reference to "in vitro" urinary metabolite profiles in claims 1 and 9 of the '715 patent is a typographical error. A person of ordinary skill in the art in the mid-1990s would understand that urinary metabolite profiles are measured using living subjects, or "in vivo." Thus, a person of ordinary skill in the art in the mid-1990s would interpret the claim terms "in vitro urinary metabolite profile" from claims 1 and 9 to mean "in vivo urinary metabolite profile," as used claim 5.

47. In my opinion, a person of ordinary skill in the art in the mid-1990s would understand "in vivo urinary metabolite profile" as used in claim 5 of the '715 patent to mean the relative amounts of Pathway 1 and Pathway 2 metabolites produced by a particular niacin formulation. In particular, the '715 patent describes the "in vivo urinary metabolite profile" for niacin as:

> [t]he percent of the dose excreted in urine as niacin and [nicotinuric acid] as well as the percent of the dose excreted in urine as metabolites other than niacin and [nicotinuric acid] relative to the total dose recovered.

'715 patent, 13:15-18.

48. I understand that Defendants have asserted that the term "in vivo urinary metabolite profile" is indefinite. I disagree. A person of ordinary skill in the art in the mid-1990s would have understood how to measure the urinary metabolites produced by a particular niacin formulation using known techniques and as described in the '715 patent. *See* '715 patent, 13:39-44 & Table 8. The relative amounts of Pathway 1 and Pathway 2 metabolites produced would be the "in vivo urinary metabolite profile" for a particular niacin formulation.

49. Moreover, a person of ordinary skill in the art in the mid-1990s would have understood that the "in vivo urinary metabolite profile" is a property of the particular niacin formulation, not the subjects used to measure the relative amounts of Pathway 1 and Pathway 2 metabolites produced. Indeed, the '715 patent repeatedly associates urinary metabolite profiles with particular niacin ***formulations***. *See* '715 patent, 13:45-14:28, Fig. 5, Table 8.

50. Accordingly, in my opinion, a person of ordinary skill in the art would have understood "in vivo urinary metabolite profile" as used in claim 5 of the '715 patent to mean "the percent of a dose of a nicotinic acid formulation excreted in urine as niacin and nicotinuric

acid and the percent of the dose excreted in urine as other metabolites relative to the total dose recovered."

51. As this case is ongoing, I may supplement the opinions expressed herein at a later date based upon further information provided to me.

I declare under the penalty of perjury that the above is true and correct.

Dated: November 15, 2011

Michael B. Bottorff, Pharm.D.

CURRICULUM VITAE

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PROFESSIONAL EXPERIENCE

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1997 – 2009	Professor of Clinical Pharmacy Division of Pharmacy Practice College of Pharmacy University of Cincinnati
1989 - 1997	Associate Professor (Chairman, 1989-94) Division of Pharmacotherapy University of Cincinnati
1988 - 1989	Associate Professor and Director of Educational Programs Department of Clinical Pharmacy University of Tennessee, Memphis
1983 - 1988	Assistant Professor Department of Clinical Pharmacy University of Tennessee, Memphis

EDUCATION AND TRAINING

Pharmacy Residency 1981 - 1983	Chief Resident Albert B. Chandler Medical Center College of Pharmacy University of Kentucky Lexington, KY
Doctor of Pharmacy 1977 - 1981	Graduated with High Distinction University of Kentucky Lexington, KY
Bachelor of Science 1972 - 1976	Graduated with Honor Industrial Management Georgia Institute of Technology Atlanta, GA

PRESENTATIONS

Invited Presentations (selected from over 900 since 1982)

1. "New inotropic agents." Michigan Society of Hospital Pharmacists, Detroit, MI -- February 1985
2. "Pharmacokinetic software for personal computers." ASHP Computer Systems Conference, Orlando, FL -- March 1985
3. "Advances in cardiovascular therapeutics." Kentucky Society of Hospital Pharmacists, Lexington, KY -- September 1985
4. "Medical management of ischemic heart disease." Virginia Society of Hospital Pharmacists, Williamsburg, VA --October 1986
5. "Clinical pharmacokinetics of antiarrhythmic agents." Norwich Eaton Research and Development, Norwich, NY -- December 1988
6. "Clinical significance of digoxin-like immunoreactive substances." ACCP Regional Symposium on Cardiovascular Therapeutics, Minneapolis, MN -- May 1989 and Pittsburgh, PN -- October 1989
7. "The current state of antiarrhythmic therapy: focus on the newer agents." Washington State Society of Hospital Pharmacists, Tacoma, WA -- October 1989
8. "Pharmacokinetic and pharmacodynamic alterations in critically ill cardiac patients." Twenty-fourth Annual American Society of Hospital Pharmacists Midyear Clinical Meeting, Atlanta, GA -- December 1989
9. "Differentiating between the calcium channel antagonists." Medical Grand Rounds, VA Medical Center, Tampa, FL -- April 1990
10. "Choosing drug therapy for the hypertensive diabetic patient." Texas Society for Hospital Pharmacists." Galveston, TX -- October 1990
11. "Calcium channel antagonists: which to use when." Pharmacy Department, Beth Israel Hospital, Newark, NJ -- November 1990
12. "A comparison of Holter monitoring vs. electrophysiologic testing for guiding the therapy of ventricular arrhythmias." ASHP Symposium on the Treatment of Arrhythmias, Las Vegas, NV -- December 1990
13. "Recent trends in antiarrhythmic therapy." Albany College of Pharmacy 13th Annual Pharmacy Practice Institute, Albany, NY -- February 1991
14. "The effects of positive inotropes on mortality in congestive heart failure." ACCP Symposium on Congestive Heart Failure, Minneapolis, MN -- August 1991
15. "Clinical pharmacology of calcium channel antagonists." Speaker and Program Moderator, ASHP Symposium on Calcium Channel Antagonists: Sustained-Release Technology, New Orleans, LA -- December 1991
16. "Variability in drug response: influence of genetics, race and stereochemistry." Symposium Moderator, APhA Annual Meeting, San Diego, CA -- March, 1992
17. "Interaction of toxicology with clinical pharmacy." Professional Practice in Clinical Toxicology: A Review, American Association of Clinical Chemists, Cincinnati, OH -- June, 1992
18. "Therapeutic dilemmas in the management of lipid disorders." Symposium Moderator at American Society of Hospital Pharmacists Exhibitor's Theater, Orlando, FL -- December, 1992

19. "Current drug therapy for acute hypertensive emergencies." Emergency Medicine Grand Rounds, University of Cincinnati Department of Emergency Medicine, Cincinnati, OH -- January 1993
20. "Management of the patient with hyperlipidemia." Pharmacy Grand Rounds, Metro Health Medical Center, Cleveland, OH -- May, 1993

21. "Evaluating drug therapy in patients with cardiovascular disorders." Two Day Workshop in Clinical Pharmacy presented at the University of Ulm Hospital, Ulm, Germany -- October 5,6 1993
22. "Risk factors for cardiovascular disease." Symposium on Lipid Therapy in the Elderly, American Society of Consultant Pharmacists, New Orleans, LA -- November, 1993
23. "Clinical pharmacology of HMG-CoA reductase inhibitors." National Lipid Education Faculty, Bristol-Myers Squibb, Orlando, FL -- April, 1994
24. "Drug therapy for lipid disorders." Medical Grand Rounds, St. Joseph Hospital, Parkersburg, WV -- April, 1994
25. "Altering the natural history of coronary artery disease." Internal Medicine Grand Rounds, Mt. Clemens General Hospital, Michigan State School of Osteopathy, Detroit, MI -- May 1994
26. "Treatment dilemma: the high-risk patient." Speaker and Symposium Moderator for "Evolving Challenges in Coronary Artery Disease: Focus on the High Risk Patient," American College of Clinical Pharmacy Annual Meeting, St. Louis, MO -- August, 1994
27. "Management of congestive heart failure." Family Practice Program, Wright-Patterson Air Force Base, Dayton, OH -- August, 1994
28. "Treatment options for patients with congestive heart failure." Fayette County Medical Society, Lexington, KY -- August, 1994
29. "Drug therapy selection for patients with lipid disorders." Pharmacy Grand Rounds, VA Medical Center, Beckley, WV -- October, 1994
30. "Medical management of patients with hyperlipidemia." Internal Medicine Grand Rounds, Bay City Medical Center, Bay City, MI -- November, 1994
31. "Treatment guidelines for congestive heart failure." American College of Clinical Pharmacy, New York Chapter, Ossining, NY -- November, 1994
32. "Principles of Geriatric Drug Therapy." 17th Annual Family Medicine Review, University of Louisville Medical School and Jewish Hospital, Louisville, KY -- April, 1995
33. "Implementation of treatment guidelines for congestive heart failure." College of Pharmacy, University of Colorado, Denver, CO -- May, 1995
34. "Beyond diuretics, ACE-inhibitors and digoxin: alternate approaches to the drug therapy for congestive heart failure." Cardiology Grand Rounds, Division of Cardiology, College of Medicine, University of Colorado, Denver, CO -- May, 1995
35. "Treatment guidelines for congestive heart failure and the Ohio State Medicaid system." CHF Care Standards Advisory Board, Tampa, FL -- May, 1995
36. "Medical management of congestive heart failure." Mid-Atlantic Consultant Pharmacists MTG, Baltimore, MD -- February, 1996
37. "Controversies in the management of heart failure." Albany College of Pharmacy, Albany, NY -- March, 1996
38. "Update on new drugs approved in 1995." University of Louisville Family Practice Symposium, Louisville, KY -- March, 1996
39. "The role of pharmacy in optimizing outcomes for patients with heart failure." Annual Meeting Ohio Pharmacists Association, Columbus, OH -- March, 1996
40. "Heart Failure: Implications for the consultant pharmacist." Purdue University Geriatrics Seminar, West Lafayette, IN -- April, 1996
41. "A disease state management approach to Medicaid patients with heart failure." Invited speaker to the Illinois Medicaid DUR Board, Chicago, IL -- April, 1996
42. "National guidelines for the diagnosis and management of heart failure." American Medical Directors Association (AMDA), Ohio Affiliate, Columbus, OH -- May, 1996
43. "Renal pharmacology of drugs used for congestive heart failure." North East Ohio College of Medicine Spring Seminar, Youngstown, OH -- May, 1996
44. "Impact of heart failure on renal hemodynamics and pharmacology." North East Ohio College of Medicine Grand Rounds, Youngstown, OH -- May, 1996
45. "Disease state management of heart failure." American Society of Consultant Pharmacists Annual Meeting, Marco Island, FL -- May, 1996

46. "Impact of new AMDA Heart Failure guidelines." Purdue University Annual Update in Pharmacy Practice, Indianapolis, IN -- July, 1996
47. "Adequacy of AHCPR heart failure guidelines." American College of Clinical Pharmacy Annual Meeting, Nashville, TN -- August, 1996
48. "Treatment of heart failure in long-term care facilities." Virginia AMDA Physicians, Norfolk, VA – October, 1996
49. "Disease state management and the drug therapy for heart failure." Maryland Medicaid DUR Board, Baltimore, MD – November, 1996
50. "Update on drug trials for the management of hyperlipidemia." American Society of Health System Pharmacists satellite symposium, New Orleans, LA – December, 1996
51. "Drug therapy selection and monitoring for the patient with heart failure." American Society of Health System Pharmacists, New Orleans, LA – December, 1996
52. "Disease state management for heart failure." Pennsylvania state Medicaid DUR Board, Harrisburg, PA – December, 1996
53. "Medicaid DUR and disease state management for heart failure." National DUR Board meeting, San Diego, CA – February, 1997
54. "The pharmacoeconomics of treating hyperlipidemia." Toledo College of Pharmacy annual CE program, Toledo, OH – April, 1997
55. "Disease state management for heart failure." Indiana Medicaid DUR Board, Indianapolis, IN – April, 1997
56. "Use of angiotensin II receptor antagonists in children." Childrens Hospital pharmacists, Cincinnati, OH – April, 1997
57. "Treating hyperlipidemia in a managed care environment." Maryland Society of Health System Pharmacists, Baltimore, MD – May, 1997
58 "The medical management of acute myocardial infarction." Directors of Pharmacy in the Los Angeles area, Los Angeles, CA – May, 1997
59 "Therapeutic frontiers for treating congestive heart failure." Family Practice Physicians Annual MTG, Family Practice Department, Medical University of South Carolina, Charleston, SC – May, 1997
60 Evidence based approach to treating hyperlipidemia. American Pharmaceutical Association Annual Meeting, Dallas, TX – August, 1997
61 Treatment guidelines for heart failure. Michigan AMDA Annual Meeting, Detroit, MI -- October, 1997
62 Treating hypertension in the elderly. American Medical Directors Assoc. Annual Meeting, San Antonio, TX – March, 1998
63 The great lipid debate. Academy of Managed Care Pharmacy Annual Meeting, Philadelphia, PA – May, 1998
64 Formulary decision making for HMG-CoA reductase inhibitors. Department of Defense, San Antonio, TX – September, 1998
65 Treating hyperlipidemia – new treatment for an old problem. Program chair and presenter, ASHP Midyear Meeting, Las Vegas, NV – December, 1998
66 Natriuretic peptides in heart failure. Program chair and presenter, ASHP Midyear Meeting, Las Vegas, NV – December, 1998
67 Angiotensin II receptor blockers for heart failure and hypertension. Program chair and presenter, ASHP Midyear Meeting, Las Vegas, NV – December, 1998
68 JNC VI guidelines for hypertension. ASHP Midyear Meeting, Las Vegas, NV – December, 1998
69 Are HMG-CoA reductase inhibitors for everyone? Lipid debate, ASHP Midyear Meeting, Las Vegas, NV – December, 1998
70 Comparison of European and NCEP treatment guidelines for hyperlipidemia. Program Moderator, ACCP Spring Meeting, Orlando, FL – April, 1999
71 The great lipid debate. Arizona Society of Hospital Pharmacists, Annual Meeting, Tucson, AZ -- July, 1998
72 Drug metabolism and HMG-CoA reductase inhibitors. A Consultants Conference, Toronto, Ontario – October, 1999
73 Ventricular tachycardia and heart failure – a lethal combination. ACCP Annual Meeting, Kansas City, Kansas – October, 1999
74 Estrogen and womens cardiovascular health. Program Moderator, ACCP Annual Meeting, Kansas City, Kansas – October, 1999

75 Betablockers are a standard of care for heart failure. ASHP Midyear Meeting, Orlando, FL – December, 1999
76 Understanding and predicting cardiovascular drug interactions. ASHP Midyear Meeting, Orlando, FL –

December, 1999

77 Vasopeptidase inhibition in hypertension and heart failure. Program Moderator and Presenter, ASHP Midyear Meeting, Orlando, FL – December, 1999

78 Cytochrome P450 mechanisms of drug interactions. Michigan APhA Annual Meeting, Detroit, MI – February, 2000

79 Managing hypertension in the diabetic patient. American Pharmaceutical Association Annual Meeting, Washington D.C. – March 2000

80 Treating hypertension to new blood pressure goals. Cincinnati area physicians, Cincinnati, OH – March, 2000

81 Modern management of heart failure: beta-blockers. American Society of Consultant Pharmacists Annual Meeting, Boston, MA – November, 2000

82 Heart failure therapy: beta-blockers. American Society of Health System Pharmacists Mid-Year Clinical Meeting, Las Vegas, NV – December, 2000

83 Statins in acute coronary syndromes. American Pharmaceutical Association Annual Meeting, San Francisco, CA – March, 2001

84 Expanding the role of statins: acute coronary syndromes. Academy of Managed Care Pharmacy Annual Meeting, Tampa, FL – April, 2001

85 Combination antiplatelet therapy for atherosclerotic disease. Kentucky Society of Hospital Pharmacists Annual Meeting, Louisville, KY – May, 2001

86 Avoiding drug interactions by understanding cytochrome P450. American Association of Physician Assistants Annual Meeting, Chicago, IL – May, 2001

87 Application of the MIRACL trial results. Wright Patterson Aif Force Base, Internal Medicine Grand Rounds, Dayton, OH – October, 2001

88 Innovations in treating dyslipidemias. VA Hospital Internal Medicine Grand Rounds, Lexington, KY – November, 2001

89 Preventing the next cardiovascular event. American Society of Health System Pharmacists Mid-Year Clinical Meeting, New Orleans, LA – December, 2001

90 Lipid management in acute coronary syndromes. Academy of Managed Care Pharmacy Annual Meeting, Salt Lake City, UT – April, 2002

91 New strategies for managing hypertension. American Society for Consultant Pharmacists North Carolina Chapter, Charlotte, NC – April, 2002

92 Using hand-held devices to manage drug-drug interactions. American Association of Physician Assistants Annual Meeting, Boston, MA – May, 2002

93 Drug therapy for the acute coronary syndrome patient. American Association of Nurse Practitioners Annual Meeting, Reno, NV – June, 2002

94 Clinically important drug interactions. Continuing Medical Education Company Winter Seminar, Phoenix, AZ – March, 2005

95 Lipid management in metabolic syndrome. DiMedex Continuing Education Seminar, New York, NY – April, 2005

96 Antiplatelet therapy in acute coronary syndromes. American Geriatric Society Annual Meeting, Orlando, FL – May, 2005

97 Drug interactions with cardiovascular drugs. Iowa Heart Center, Des Monies, IA – June, 2005

98 Statin safety and drug interactions. National Lipid Association Statin Safety Task Force, Washington, DC – July, 2005

99 NCEP goal attainment with statin therapy. PharmMed Continuing Education Seminar, Boston, MA – October, 2005

100 Meeting NCEP treatment guidelines: primary and secondary goals. American Society of Health System Pharmacists, Las Vegas, NV – Dec, 2005

101 Combination antiplatelet therapy for patients with ACS. American Pharmaceutical Association Annual Meeting, San Francisco, CA – March, 2006

102 Update in the medical management of heart failure. Albany College of Pharmacy Annual CE Program, Albany, NY – June, 2006

103 Compliance with lipid medications: a primer for pharmacists. PharmMed CE for Pharmacists, Boston, MA – October, 2006

104 The NLA statin safety report. Deleware Cardiology Annual CE, Wilmington, DE – November, 2006

105 Aggressive management of lipid disorders. American Society of Health System Pharmacists, Orlando, FL – December, 2006

106 Statin selection: issues of efficacy and safety. Wright Patterson AirForce Internal Medicin Grand Rounds,

Dayton, OH – February, 2007

107 New cardiovascular therapies. Michigan Pharmacists Association Annual Meeting, Detroit, MI – March, 2007

108 Promoting compliance with lipid therapies. National Lipid Association Masters Review Course, Phoenix, AZ – May, 2007

109 Optimizing outcomes in patients with metabolic syndrome. University of Cincinnati Interdisciplinary Conference, Greenbriar, WV – November, 2007

110 Safety of antiplatelet therapy in the elderly population. American Society of Consultant Pharmacists Annual Meeting, Philadelphia, PA – November, 2007

111 New AHA guidelines for ACS. American Society of Health System Pharmacists Annual Meeting, Las Vegas, NV – December, 2007

Scientific Presentations: *(Not published as abstracts)*

1. "Tobramycin distribution in pericardial fluid, heart tissues and serum in patients undergoing cardiac surgery." Seventeenth Annual American Society of Hospital Pharmacists Midyear Clinical Meeting, Los Angeles, CA -- December 1982
2. "Nifedipine stability in cardioplegic solutions." Eighteenth Annual American Society of Hospital Pharmacists Midyear Clinical Meeting, Atlanta, GA -- December 1983
3. "In-vitro determination of lidocaine protein binding in preeclamptic patients." Annual Meeting of the Society of Perinatal Obstetricians, San Antonio, TX -- January 1986
4. "Bayesian vs. least square methods for aminoglycoside TDM." Twenty-first Annual American Society of Hospital Pharmacists Midyear Clinical Meeting, Las Vegas, NV -- December 1986
5. "The clinical significance of digoxin-like immunoreactive substances." Department of Pharmacy Practice Research Seminar Series, Wayne State University, Detroit, MI -- February 1987
6. "The pharmacology of DLIS." Division of Cardiology Research Grand Rounds, Wayne State University, Detroit, MI -- April 1987
7. "The effects of diltiazem on oxidative drug metabolism." Ohio Conference on Clinical Pharmacy and Clinical Pharmacology, Columbus, OH -- October 1989
8. "The contribution of polymorphic drug metabolism to the pharmacodynamic response of metoprolol." Cardiology Research Seminars, Division of Cardiovascular Diseases University of Cincinnati College of Medicine -- August 1990
9. "Future trends in cardiovascular drug research." Florida Society of Hospital Pharmacists Annual Meeting, Tarpon Springs, FL -- May 1991
10. "Heart rate response to exercise for evaluating pharmacodynamic response to stereoselective drug metabolism." Annual Meeting of the Ohio Conference on Clinical Pharmacy and Clinical Pharmacology, Toledo, OH -- November 1991
11. "Stereoselective pharmacokinetics and pharmacodynamics of the CYP2D6 metabolic pathway: studies with metoprolol." University of Kentucky Research Seminar Series, Lexington, KY -- February 1992
12. "Assessing pharmacodynamics of antiarrhythmic agents." American College of Clinical Pharmacy Pharmacodynamic Symposium, Toronto, Canada -- August, 1992
13. "The influence of CYP2D6 inhibition with quinidine on valproic acid pharmacokinetics." Ohio College of Clinical Pharmacy Annual Meeting, Cincinnati, OH -- October, 1992
14. "Stereoselective aspects of CYP2D6 metabolism." Research Seminar Series, Division of Clinical Pharmacology, Indiana University Medical School, Indianapolis, IN -- November, 1992
15. "Differences in drug metabolism between HMG-CoA reductase inhibitors." Scientific Session for the National Pharmacy Cholesterol Council, Orlando, FL -- December, 1992
16. "Pharmacodynamic modeling in cardiovascular pharmacology." Scientific Symposium for the American College of Clinical Pharmacy Winter Forum, Ft. Lauderdale, FL -- February, 1993
17. "Hepatic metabolism of the HMG-CoA reductase inhibitors lovastatin and simvastatin is CYP3A-dependent." Lipid Education Symposium on Issues in Lipid Education in the 1990's: Therapeutic Considerations, San Diego, CA -- March, 1993
18. "Molecular mechanisms of drug metabolism and its application to predicting drug interactions." College of Pharmacy Research Seminar Series, University of Kentucky, Lexington, KY -- September, 1993
19. "Molecular mechanisms of significant drug interactions with the HMG-CoA reductase inhibitors." Squibb Research Institute, Atlanta, GA -- October, 1993
20. "Predicting drug interactions with HMG-CoA reductase inhibitors." Family Practice Grand Rounds, Jewish

Hospital, Louisville, KY -- November, 1993

21. "Predicting and understanding drug interactions involving the cytochrome P450 system." Cardiology Grand Rounds, University of Cincinnati Medical Center, Cincinnati, OH -- April, 1994
22. "Molecular biology, drug metabolism and drug interactions." Research Seminar Series, Department of Pharmacy Practice, Ohio State University College of Pharmacy, Columbus, OH -- Sept, 1994
23. "From molecular biology to the bedside: prediction of drug interactions." University of Cincinnati College of Pharmacy Research Seminars, Division of Pharmaceutical Sciences, Cincinnati, Ohio -- January, 1995
24. "Advances in congestive heart failure: an opportunity for future research." Department of Clinical Pharmacy, University of Tennessee College of Pharmacy, Memphis, TN -- June, 1995
25. "Medical advances in the treatment of congestive heart failure: research that focuses on patient outcomes." College of Pharmacy, State University of New York at Buffalo, Buffalo, NY -- July, 1995
26. "Pharmacokinetic and pharmacodynamic modeling." Symposium Moderator, ACCP Winter Meeting, Monterey, CA -- February, 1996
27. Understanding and predicting clinically important drug-drug interactions: the role of Cytochrome P450. University of Georgia College of Pharmacy Seminar Series, Augusta, GA – August, 1997
28. Understanding and predicting clinically important drug-drug interactions: the role of Cytochrome P450. Turkish Cardiology Congress, Istanbul, Turkey – June, 1998
29. Understanding and predicting clinically important drug-drug interactions: the role of Cytochrome P450. Turkish Endocrinology Congress, Istanbul, Turkey – October, 1998
30. Understanding and predicting clinically important drug-drug interactions: the role of Cytochrome P450. South American Cardiology Congress, Cartegena, Colombia – November, 1998
31. Understanding and predicting clinically important drug-drug interactions: the role of Cytochrome P450. European Cardiology Congress, Lisbon, Portugal – February, 1999
32. Understanding and predicting clinically important drug-drug interactions: the role of Cytochrome P450. University of Pittsburgh Division of Cardiology Grand Rounds, Pittsburgh, PA – December, 1999
33. Drug interactions and the cytochrome P450 system: how to predict and prevent. St. Louis University Cardiovascular Symposium, St. Louis, MO – April, 2000
34. Complexities of heart failure drug management. Ohio State College of Pharmacy Cardiovascular Symposium, Columbus, OH – April, 2000
35. Clinical pharmacology of statins. Lakewood Hospital Grand Rounds, Cleveland, OH – May, 2000
36. Vasopeptidase inhibition: a new class of drug for heart failure and hypertension. Good Samaritan Hospital Grand Rounds, Dayton, OH – May, 2000
37. Cytochrome P450 as a mechanism of clinically important drug interactions. University of Chicago Medical Grand Rounds, Chicago, IL – May, 2000
38. Innovations in heart failure and hypertension: vasopeptidase inhibition. Doctors Hospital Medical Grand Rounds, Columbus, OH – May, 2000
39. Combining neutral endopeptidase inhibition with ACE-inhibition for hypertension and heart failure. University of Washington Cardiology Grand Rounds, Seattle, WA – May, 2000
40. Cytochrome P450 principles to predict drug-drug in-vivo drug-drug interactions. American College of Clinical Pharmacy Indiana Chapter, Indianapolis, IN – November, 2000
41. How to predict and prevent drug interactions through cytochrome P450. Medical Society of Deleware, Newark, DE – November, 2000
42. Cardiovascular drug interactions. Cleveland Clinic Department of Preventative Cardiology, Cleveland, OH – January, 2001
43. Advances in the therapeutics of acute myocardial infarction. American College of Clinical Pharmacy Michigan Chapter, Traverse City, MI – April, 2001
44. Cardiovascular risk reduction. Cardiology Grand Rounds, Bethesda North Hospital, Cincinnati, OH – September, 2001
45. Cytochrome P450 and predicting drug interactions. University Hospitals of Cleveland Medical Grand Rounds, Cleveland, OH – November, 2001
46. Understanding and predicting clinically important drug-drug interactions. Case Western Reserve Cardiology Grand Rounds, Cleveland, OH – March, 2002
47. Clinically important drug-drug interactions for endocrinologists. Indiana Society of Endocrinologists, Indianapolis, IN – April, 2002
48. The future of therapeutic interventions for raising HDL. University of Alabama Department of Cardiology Visiting Professorship, Birmingham, AL – May, 2006
49. Understanding and predicting cytochrome P450-based drug interactions. Nebraska Cardiology Consultants, Omaha, NE – March, 2007

AWARDS

Academic All-American (basketball), Georgia Tech -- 1976
Rho-Chi President, University of Kentucky -- 1979-80
Jefferson County Academy of Pharmacy Award, University of Kentucky -- 1979
Eli Lilly Achievement Award, University of Kentucky -- 1980
Crawford E. Meyer Award, University of Kentucky -- 1980
Chief Pharmacy Resident, University of Kentucky -- 1982-3
Outstanding Pharmacy Resident, University of Kentucky -- 1983
Outstanding Paper in Clinical Research, Conference of Residents, Omaha, NE--1983
Impact Award, University of Kentucky Residency Program --1983
Outstanding Clinical Pharmacy Educator, University of Tennessee -- 1984
Recipient, Preceptor for American College of Clinical Pharmacy-Merck Cardiovascular Fellowship-- 1985
Academic Challenge Fellowship Award, University of Cincinnati -- 1989-91
Astra Pharmaceuticals Award for Clinical Pharmacy Research, University of Cincinnati -- 1989
Outstanding Didactic Instructor, Pharm.D. Program, University of Cincinnati -- 1990, 1994
Who's Who in Health and Medical Services -- 1990
Speaker, Abstract Plenary Session ACCP Annual Meeting -- 1990
Fellow Recognition, American College of Clinical Pharmacy – 1991
Rho Chi Award for Teaching Excellence, University of Cincinnati – 2000
Faculty Excellence Award for Teaching, P2 students, University of Cincinnati-- 2004
Rho Chi Award for Teaching Excellence, University of Cincinnati -- 2006

PROFESSIONAL ORGANIZATIONS

Rho Chi Honor Society
American Association of Colleges of Pharmacy (1983-89)
American College of Clinical Pharmacy (Full Member, 1985-2007)
- Member, Educational Affairs Committee (1988-89)
- Chairman, Educational Affairs Committee (1989-90)
- Nominee, Board of Regents (1990, 1994)
- Member, Nominations Committee (1990-92)
- ACCP Fellow (1991)
- Chair, Abstract Review Committee for Winter Meeting (1993)
- Vice-Chair, Awards Committee (1993)
- Chair, Awards Committee (1994)
- Member, Winter Program Committee (1995)
- Chair, 1998 Annual Program Committee (1997)
- Member, Scientific Abstract Award Committee (1997)

American Heart Association (1983-89, 2008-Present)
American Society for Clinical Pharmacology and Therapeutics (1985-1999)
American Pharmaceutical Association (1990-93)
- Chair-Elect, Clinical Section, Academy for Pharmaceutical Research and Science (1991)
- Chairman, Clinical Section, Academy for Pharmaceutical Research and Science (1992)
- Member, Educational Program Committee, 1992 Meeting
- Member, Policy Committee (1992)

National Lipid Association (2006-Present)
- Midwest Board of Directors (2006-2008)

JOURNAL REFEREE/EDITORIAL BOARDS

Editorial Advisory Board:

Journal of Applied Therapeutic Research
Pharmacotherapy (1998-2007)
Cardiology Review
Journal of Clinical Lipidology (2007-present)

Journal Referee:
Biopharmaceutics and Drug Disposition
Journal of Pharmaceutical Sciences
American Journal of Hospital Pharmacy
Chest
Pharmacotherapy
DICP, Annals of Pharmacotherapy
Hospital Formulary
Archives of Internal Medicine
American Journal of Pharmaceutical Education
Clinical Pharmacy
American Journal of Cardiology
Journal of Cardiovascular Pharmacology
Drugs and Aging
Drug Safety

COMMITTEES

Committees - University of Cincinnati (1989-Present):

Chair, Admissions Committee 2006-Present
Member, Division Research and Scholarship Committee, 2000-2005
Chair, College ARPT Committee, 2000-2002
Member, Ad Hoc Committee on New Masters Program, 2001-Present
Member, Strategic Planning Committee 2000
Member, Curriculum Committee 1999-2000
Member, Pharmacoeconomics Faculty Search Committee 1999-2000
Member, Admissions Committee 1999-2000
Member, Ad Hoc College Space Committee, 1997
Member, Task Force for Strengthening MS/PhD Programs, 1997-98
Member, Biopharmaceutics Faculty Search Committee, 1997
Member, Dean Search Committee, College of Pharmacy, 1995-96
Member, Academic Programs Committee, Division of Pharmacy Practice, 1989-Present
Member, Pharmacology Task Force, College of Medicine, 1994
Member, Executive Committee, College of Pharmacy, 1989-1996
Member, Pharm.D. Program Admissions Committee, 1991-94
Member, College of Pharmacy Appointment, Reappointment, Promotion and Tenure Committee, 1992-Present (Chair, 1993-Present)
Member, College Space Utilization Ad Hoc Committee, 1997-1999
Chair, Task Force on Professional Experience Programs, 1993-94
Chair, ACPE Self-Study Committees on College Administration and Clinical Programs, 1993-94
Member, Medical Center Task Force on Focus Area Review, 1992-93
Member, New Drug Evaluation Unit Review Task Force, 1992
Chairman, College Strategic Planning Non-Academic Internal Audit Committee, 1989-91
Member, Capital Equipment Committee, College of Pharmacy, 1989-91
Chair, Curriculum Committee, College of Pharmacy, 1989-91
Chair, Faculty Search Committee, Division of Pharmacotherapy, 1989-90, 1990-91
Member, Pharm.D. Planning Committee, College of Pharmacy, 1990-91
Member (alternate), ARPT Committee, College of Pharmacy, 1989-90
Member, Clinical Pharmacists Search Committee, University Hospital, 1991, 1992
Member, University Council on General Education, 1991-93
Member, Space Committee, College of Pharmacy, 1991-92

Member, Pharm.D. Selection Committee, College of Pharmacy, 1990-91, 1991-92
Leader, Focus Group Discussion on Pharmacotherapy, Curriculum Review Task Force, 1992

Committees - National:

Board of Directors, MidWest Lipid Association 2006-2007
Member, Inter-disciplinary Council, 2001-2006
Chair, National Pharmacy Cardiovascular Council 2000-2007
Chair, ACCP 1998 Annual Program Committee
Chair & Past-Chair, Cardiology Practice & Research Network, American College of Clinical Pharmacy 1998-00
Member, ACCP Scientific Abstract Award Committee, 1997
Vice-Chair, Parke-Davis Pharmacy CE Advisory Board for Hyperlipidemia
Member, Hypertension Advisory Board, Bristol-Myers Squibb, 1996-Present
Member, Cardiac Advisory Board, Bristol-Myers Squibb, 1995-Present
Member, CHF Care Standards Advisory Board, Merck and Co., 1995-1998
Chair, Heart Failure Consensus Panel, State of Ohio Medicaid DUR Board, 1994-1997
Member, National Clinical Pharmacy Cholesterol Council, 1990-Present
Vice-Chair, 1996-Present
Member, Federal Agency for Health Care Policy and Research, Expert Panel on Congestive Heart Failure, 1992-1994
Member, Expert Panel on CHF in the Elderly, Managed Care Resources, 1992-93
Chair, Midwestern Pharmacy Cholesterol Council, 1991-93
Vice Chair, ACCP Awards Committee, 1993
Chair, ACCP Awards Committee, 1994
Member, ACCP Winter Program Committee, 1995
Member, ASHP Cardiovascular Fellowship Review Panel, 1987, 1988, 1990, 1991, 1992
Member, ACCP Educational Affairs Committee, 1988-89
Member, ACCP Cardiovascular Fellowship Review Panel, 1989, 1995, 1996
Chair, ACCP Educational Affairs Committee, 1989-90
Member, Abstract Review Committee, ACCP Annual Meeting, 1987, 1988, 1989,1990, 1991, 1992, 1994, 1995, 1996, 1997, 1998, 1999, 2000
Winter Meeting 1994, 1996, 1997, 1998, 1999, 2000
Member, ACCP Grant Review Committee, 1994,1995
Member, AACP Task Force on Pharm.D. Curricula, 1990-91
Member, ACCP Nominations Committee, 1990-91, 1991-92
Chair-elect, APhA Clinical Section of the APRS, 1991
Chair, APhA Clinical Section of the APRS, 1992
Member, APhA Education Committee (Annual Meeting Program), 1991-92
Member, Grant Selection Committee, Astra Clinical Pharmacy Research Award, 1991

CONSULTING

Scribner Medical Productions, 1989-1992
Norwich Eaton Pharmaceuticals, Cardiovascular Research Group, 1989-1992
Omnicare, 1994-2006
CHF Care Standards Advisory Board, Merck Human Health Division, 1995-1998
International Cardiovascular Advisory Board, Bristol-Myers Squibb, 1995-2005
State Medicaid DUR Boards for Ohio, Indiana, Illinois, Pennsylvania and Maryland (1994-1999)

OTHER ACTIVITIES

Faculty Preceptor for Dr. Margaret Whidden, Resident in Adult Medicine Department of Clinical Pharmacy, 1984-85
Faculty Preceptor for Dr. Timothy J. Hoon, ACCP-Merck Fellow in Cardiovascular Pharmacokinetics

and Therapeutics, 1985-87
Faculty Preceptor for Dr. David Kazierad, Research Fellow in Cardiovascular Pharmacokinetics and Therapeutics, 1987-89
Faculty Preceptor for Karen Schlanz, Research Fellow in Cardiovascular Pharmacokinetics and Pharmacodynamics, 1989-91
Team Leader, American Heart Association Research Funds Teleparty, Cincinnati, Ohio -- November, 1993
Research Sabbatical 1999
Thesis Committee, Sharon Haines, Ph.D. in clinical pharmacology, School of Nursing, 1998-2000
Certified Masters in Lipidology 2007

GRANTS AND CONTRACTS RECEIVED

1. Therapeutic Drug Monitoring Education for Clinical Chemists ($66,000). Abbott Laboratories, 1983; Co-Investigator (Dr. William Evans, PI).
2. Clofibrate Induced Acetylation of Procainamide ($5,000). American Heart Association, Tennessee Affiliate, 1984; Principal Investigator.
3. Evaluation of Fluorescence Polarization Immunoassays for Digoxin, Procainamide, Ethosuximide and Acetaminophen ($12,000). Abbott Laboratories, 1984; Principal Investigator.
4. Clindamycin Disposition in Patients Undergoing Cardiac Surgery ($2,000). The Upjohn Company, 1984; Principal Investigator.
5. Urapidil in the Treatment of Hypertensive Urgencies ($40,000). Marion Laboratories, 1985; Co-Principal Investigator.
6. Grant to Develop and Test New Assays for Therapeutically Monitored Drugs ($162,000). Abbott Laboratories, 1984-1987; Co-Principal Investigator.
7. Fluorescence Polarization Immunoassay vs HPLC for Flecainide Acetate In Biological Fluids ($6,000). Abbott Laboratories, 1986; Principal Investigator.
8. Na/K ATPase Inhibition By Digitalis-Like Factors in Neonates ($10,000). American Heart Association, Tennessee Affiliate, 1986; Principal Investigator.
9. Age Relationship of DLIS in Neonates ($5,000). LeBonheur Small Grants Program, 1985; Co-Investigator (Dr. Stephanie Phelps, PI).
10. DLIS Evaluation in Neonates ($5,000). ASHP Research and Education Foundation, 1985; Co-Investigator (Dr. Stephanie Phelps, PI).
11. ACCP-Merck Fellowship Award in Cardiovascular Pharmacotherapeutics ($19,500), 1985; Principal Investigator.
12. The Effect of Diltiazem on the Pharmacokinetics and Pharmacodynamics of Encainide and its Active Metabolites ($5,000). Bristol-Meyers, 1987; Principal Investigator.
13. The Effect of Cimetidine on the Disposition of Labetalol Stereoisomers ($33,000). Smith, Kline and French Laboratories, 1987; Co-Investigator (Dr. Richard Lalonde, PI).
14. Indocyanine Green Clearance To Estimate Hepatic Blood Flow in Gastric Bypass Patients ($25,000). Janssen Pharmaceuticals, 1987; Co-Investigator (Dr. Schedawie, PI).
15. The Effect of Cimetidine on the Disposition of Dilevalol ($89,000). Schering Pharmaceuticals, 1987; Co-Principal Investigator (Dr. Richard Lalonde, PI).
16. Stereospecific Inhibition of Propranolol Metabolism: A Comparison of Verapamil and Diltiazem ($19,000). Marion Laboratories, 1988; Co-Investigator (Dr. Richard Lalonde, PI).
17. University of Tennessee-Marion Laboratories Research Fellowship ($25,000). Marion Laboratories, 1988-89; Co-Preceptor (Dr. Richard Lalonde, PI).
18. Quinidine and the Pharmacokinetics and Pharmacodynamics of Hepatic Drug Oxidative Metabolism ($7500). Astra Pharmaceuticals, 1989; Principal Investigator.
19. Academic Challenge Fellowship Award ($50,000). University of Cincinnati, 1989-91; Principal Investigator. (Fellowship support from Dean's office)
20. Stereoselective Aspects of Quinidine Inhibition of Hepatic Drug Metabolism ($8500). University of Cincinnati Research Council, 1990; Principal Investigator.
21. Introduction to Therapeutic Drug Monitoring ($4,500). Abbott Diagnostics Division, 1990; Principal Investigator.
22. The pharmacokinetics and pharmacodynamics of LNF-209, a new cardiotonic agent ($33,000). Norwich Eaton Pharmaceuticals, 1991; Principal Investigator.

23. Cholesterol Awareness Training Program for Pharmacists ($17,000). Squibb U.S. Pharmaceutical Group, 1992; Principal Investigator.
24. Quinidine as a probe for evaluating polymorphic drug metabolism of valproic acid ($1000). Abbott Laboratories, 1992; Principal Investigator.
25. The influence of age on stereoselective renal excretion and organic cation/proton antiport activity. Astra Pharmaceuticals ($10,000), American Diabetes Foundation ($5000), and University of Cincinnati Academic Challenge ($5000); 1992; Co-Principal Investigator.
26. Mechanisms of lidocaine induced elevation in defibrillation threshold and its reversibility ($30,000). American Heart Association, Ohio Affiliate, 1992; Co-Investigator (Dr. Michael Ujhelyi, PI).
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EDITORIALS

SPECIAL ARTICLE

ORIGINAL INVESTIGATIONS

Special Article

Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults

The Expert Panel

• This report of an expert panel of the National Cholesterol Education Program provides new guidelines for the treatment of high blood cholesterol in adults 20 years of age and over. Total cholesterol levels are classified as follows: <200 mg/dL—"desirable blood cholesterol"; 200 to 239 mg/dL—borderline–high blood cholesterol; ≥240 mg/dL—high blood cholesterol. The guidelines detail which patients should go on to have lipoprotein analysis, and which should receive cholesterol-lowering treatment on the basis of their low density lipoprotein (LDL)–cholesterol levels and status with respect to other coronary heart disease risk factors. Dietary therapy is the primary cholesterol-lowering treatment. The report specifies the LDL-cholesterol levels at which dietary therapy should be started and the goals of therapy, and provides detailed guidance on the nature of the recommended dietary changes. If, after six months of intensive dietary therapy, LDL-cholesterol exceeds specified levels, drug treatment should be considered.

(*Arch Intern Med* 1988;148:36-69)

OVERVIEW AND SUMMARY

Increased blood cholesterol levels, or, more specifically, increased levels of low density lipoprotein (LDL)–cholesterol, are causally related to an increased risk of coronary heart disease (CHD). Coronary risk rises progressively with an increase in cholesterol level, particularly when cholesterol levels rise above 200 mg/dL (for Système International [SI] conversions throughout text, refer to Appendix I, Table 1). There is also substantial evidence that lowering total and LDL-cholesterol levels will reduce the incidence of CHD.

Two approaches can be used to lower blood cholesterol levels. The first is the subject of this report: a patient-based approach that seeks to identify individuals at high risk who will benefit from intensive intervention efforts. The goal here is to establish criteria that define the candidates for medical intervention and to provide guidelines on how to detect, set goals for, treat, and monitor these patients over time. The second approach, the population (public health) strategy, aims to shift the distribution of cholesterol levels in the entire population to a lower range. These two approaches are complementary and, together, represent a coordinated strategy aimed at reducing cholesterol levels and coronary risk.

Case finding: Initial Classification by Total Blood Cholesterol (Table 1)

Serum total cholesterol should be measured in all adults 20 years of age and over at least once every five years; this measurement may be made in the nonfasting state. Levels below 200 mg/dL are classified as "desirable blood cholesterol," those 200 to 239 mg/dL as "borderline–high blood cholesterol," and those 240 mg/dL and above as "high blood cholesterol." The cutpoint that defines high blood cholesterol (240 mg/dL) is a value above which risk of CHD rises steeply, and corresponds approximately to the 75th percentile for the adult US population. The cutpoints recommended in this report are uniform for adult men and women of all ages.

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From the National Cholesterol Education Program, National Heart, Lung, and Blood Institute, Bethesda, Md.

Reprint requests to Coordinator, National Cholesterol Education Program, National Heart, Lung, and Blood Institute, Bldg 31, Room 4A 05, Bethesda, MD 20892 (Dr Cleeman).

Table 1.—Initial Classification and Recommended Followup Based on Total Cholesterol*

Classification, mg/dL	
<200	Desirable blood cholesterol
200 to 239	Borderline–high blood cholesterol
≥240	High blood cholesterol
Recommended followup	
Total cholesterol, <200 mg/dL	Repeat within five years
Total cholesterol, 200-239 mg/dL	
Without definite CHD or two other CHD risk factors (one of which can be male sex)	Dietary information and recheck annually
With definite CHD or two other CHD risk factors (one of which can be male sex)	Lipoprotein analysis; further action based on LDL-cholesterol level
Total cholesterol ≥240 mg/dL	

*CHD indicates coronary heart disease; LDL, low density lipoprotein.

Table 2.—Classification and Treatment Decisions Based on LDL-Cholesterol*

Classification, mg/dL		
<130	Desirable LDL-cholesterol	
130 to 159	Borderline-high-risk LDL-cholesterol	
≥160	High-risk LDL-cholesterol	
	Initiation Level, mg/dL	**Minimal Goal, mg/dL**
Dietary treatment		
Without CHD or two other risk factors†	≥160	<160‡
With CHD or two other risk factors†	≥130	<130§
Drug treatment		
Without CHD or two other risk factors†	≥190	<160
With CHD or two other risk factors†	≥160	<130

*LDL indicates low density lipoprotein; CHD, coronary heart disease.

†Patients have a lower initiation level and goal if they are at high risk because they already have definite CHD, or because they have any two of the following risk factors: male sex, family history of premature CHD, cigarette smoking, hypertension, low high density lipoprotein (HDL)–cholesterol, diabetes mellitus, definite cerebrovascular or peripheral vascular disease, or severe obesity.

‡Roughly equivalent to total cholesterol level of <240 mg/dL‡ or <200 mg/dL.

§As goals for monitoring dietary treatment.

Along with cholesterol testing, all adults should also be evaluated for the presence of other CHD risk factors, including hypertension, cigarette smoking, diabetes mellitus, severe obesity, and a history of CHD in the patient or of premature CHD in family members. Patients with other risk factors should be given other forms of preventive care as appropriate.

Patients with desirable blood cholesterol levels (<200 mg/dL) should be given general dietary and risk reduction educational materials, and advised to have another serum cholesterol test within five years. Patients with cholesterol levels 200 mg/dL or greater should have the value confirmed by repeating the test; the average of the two test results is then used to guide subsequent decisions. Patients with high blood cholesterol (≥240 mg/dL) should undergo lipoprotein analysis, as should those with a borderline–high blood cholesterol (200 to 239 mg/dL) who are at high risk because they have definite CHD or two other CHD risk factors; in this report male sex is considered a risk factor for the purpose of estimating risk status. Patients with confirmed borderline–high blood cholesterol levels who do not have CHD or two other risk factors do not need further evaluation and active medical therapy; they should be given the dietary information designed for the general population and reevaluated at one year.

Some experts believe that patients in the borderline–high blood cholesterol group who have one other risk factor (eg, hypertension), or who are of younger age (20 to 39 years), should also undergo lipoprotein analysis. Although this is not recommended here as a general approach for the borderline–high blood cholesterol group, it is clear that individualized clinical judgment and patient management is appropriate for this group.

Deciding to Treat: Classification by LDL-Cholesterol (Table 2)

Once someone is identified as requiring lipoprotein analysis, the focus of attention should shift from total cholesterol to LDL-cholesterol. The ultimate objective of case finding and screening is to identify individuals with elevated LDL-cholesterol levels. Similarly, the specific goal of treatment is to lower LDL-cholesterol levels. Hence, the level of LDL-cholesterol will serve as the key index for clinical decision making about cholesterol-lowering therapy.

Lipoprotein analysis involves measurement of the fasting levels of total cholesterol, total triglyceride, and high density lipoprotein (HDL)–cholesterol. From these values, LDL-cholesterol is calculated as follows: LDL-Cholesterol = Total Cholesterol − HDL-Cholesterol − (Triglyceride/5).

Levels of LDL-cholesterol of 160 mg/dL or greater are classified as "high-risk LDL-cholesterol," and those 130 to 159 mg/dL as "borderline–high-risk LDL-cholesterol." Patients with high-risk LDL-cholesterol levels, and those with borderline-high-risk LDL-cholesterol levels who have definite CHD or two other risk factors (one of which can be male sex), should have a complete clinical evaluation and then begin cholesterol-lowering treatment. A basic principle adopted in this report is that the presence of other risk factors or definite CHD warrants initiating treatment at lower LDL-cholesterol levels and the setting of lower LDL-cholesterol treatment goals. In this scheme, a low level of HDL-cholesterol (below 35 mg/dL) is considered another risk factor (like hypertension) that will affect the assessment of overall coronary risk, and, in this way, influence clinical decisions about treatment.

The clinical evaluation should include a complete history, physical examination, and basic laboratory tests. This workup will aim to determine whether the high LDL-cholesterol level is secondary to another disease or a drug, and whether or not a familial lipid disorder is present. The patient's total coronary risk and clinical status, as well as age and sex, should be considered in developing a cholesterol-lowering treatment program.

Dietary Treatment

Treatment begins with dietary therapy. The minimal goals of therapy are to lower LDL-cholesterol to levels below the cutpoints for initiating therapy, ie, to below 160 mg/dL, or to below 130 mg/dL if definite CHD or two other CHD risk factors are present. Ideally, even lower levels of LDL-cholesterol should be attained, if possible, to achieve a further reduction in risk.

Although the goal of therapy is to lower the LDL-

cholesterol level, most patients can be managed during dietary therapy on the basis of their total cholesterol levels. This has the advantage of avoiding the additional costs and the need for a fasting blood specimen involved in the measurement of LDL-cholesterol levels. Serum total cholesterol levels of 240 and 200 mg/dL correspond roughly to LDL-cholesterol levels of 160 and 130 mg/dL, respectively. Thus, the monitoring goals during dietary therapy are to lower the serum total cholesterol level to below 240 mg/dL for patients with an LDL-cholesterol goal of <160 mg/dL, or to below 200 mg/dL for patients with an LDL-cholesterol goal of <130 mg/dL.

The general aim of dietary therapy is to reduce elevated cholesterol levels while maintaining a nutritionally adequate eating pattern. Dietary therapy should occur in two steps, the Step-One and Step-Two Diets, that are designed to progressively reduce intakes of saturated fatty acids and cholesterol, and to promote weight loss in patients who are overweight by eliminating excess total calories. The Step-One Diet should be prescribed and explained by the physician and his or her staff. This diet involves an intake of total fat less than 30% of calories, saturated fatty acids less than 10% of calories, and cholesterol less than 300 mg/d. The Step-Two Diet, used if the response to the Step-One Diet is insufficient, calls for a further reduction in saturated fatty acid intake to less than 7% of calories and in cholesterol to less than 200 mg/d. The Step-One Diet calls for the reduction of the major and obvious sources of saturated fatty acids and cholesterol in the diet; for many patients this can be achieved without a radical alteration in dietary habits. The Step-Two Diet requires careful attention to the whole diet so as to reduce intake of saturated fatty acids and cholesterol to a minimal level compatible with an acceptable and nutritious diet. Involvement of a registered dietitian is very useful, particularly for intensive dietary therapy such as the Step-Two Diet.

After starting the Step-One Diet, the serum total cholesterol level should be measured and adherence to the diet assessed at four to six weeks and at three months. If the total cholesterol monitoring goal is met, then the LDL-cholesterol level should be measured to confirm that the LDL goal has been achieved. If this is the case, the patient enters a long-term monitoring program, and is seen quarterly for the first year and twice yearly thereafter. At these visits total cholesterol levels should be measured, and dietary and behavior modifications reinforced.

If the cholesterol goal has not been achieved with the Step-One Diet, the patient should generally be referred to a registered dietitian. With the aid of the dietitian, the patient should progress to the Step-Two Diet, or to another trial on the Step-One Diet (with progression to the Step-Two Diet if the response is still not satisfactory). On the Step-Two Diet, total cholesterol levels should again be measured and adherence to the diet assessed after four to six weeks and at three months of therapy. If the desired goal for total cholesterol (and for LDL-cholesterol) lowering has been attained, long-term monitoring can begin. If not, drug therapy should be considered. A minimum of six months of intensive dietary therapy and counseling should usually be carried out before initiating drug therapy; shorter periods can be considered in patients with severe elevations of LDL-cholesterol (>225 mg/dL) or with definite CHD. Drug therapy should be added to dietary therapy, and not substituted for it.

Drug Treatment

Drug therapy should be considered for an adult patient who, despite dietary therapy, has an LDL-cholesterol level of 130 mg/dL or higher if the patient does not have definite CHD or two other risk factors (one of which can be male sex). If the patient does have definite CHD or two other risk factors, then drug therapy should be considered at LDL-cholesterol levels of 160 mg/dL or higher. The goals of drug therapy are the same as those of dietary therapy: to lower LDL-cholesterol to below 160 mg/dL, or to below 130 mg/dL if definite CHD or two other risk factors are present. These are minimal goals; if possible, considerably lower levels of LDL-cholesterol should be attained.

Individualized clinical judgment is needed for patients who do not meet these criteria for drug therapy, but have not attained their minimal goals on dietary therapy. These patients include those without definite CHD or two other risk factors whose LDL-cholesterol levels remain in the range of 160 to 190 mg/dL, and patients with CHD or two other risk factors whose LDL-cholesterol levels remain in the range of 130 to 160 mg/dL, on adequate dietary therapy. In general, maximal efforts should be made in this group to achieve lower cholesterol levels and lower CHD risk by means of nonpharmacologic approaches. Consideration should also be given to the use of low doses of bile acid sequestrants in these patients, especially in males. Moreover, many experts feel that patients with definite CHD should receive drug therapy if their minimal LDL-cholesterol goal (<130 mg/dL) has not been reached.

The drugs of first choice are the bile acid sequestrants (cholestyramine, colestipol) and nicotinic acid. Both cholestyramine and nicotinic acid have been shown to lower CHD risk in clinical trials, and their long-term safety has been established. However, these drugs require considerable patient education to achieve effective adherence. Nicotinic acid is the preferred drug in patients with concurrent hypertriglyceridemia (triglyceride levels ≥250 mg/dL), because bile acid sequestrants tend to increase triglyceride levels.

A new class of drugs, to be considered after the bile acid sequestrants and nicotinic acid, is the 3-hydroxy-3-methyl glutaryl coenzyme-A (HMG CoA) reductase inhibitors (eg, lovastatin). These drugs are very effective in lowering LDL-cholesterol levels, but their effects on CHD incidence and their long-term safety have not yet been established.

Other available drugs include gemfibrozil, probucol, and clofibrate. Gemfibrozil and clofibrate are fibric acid derivatives; they are primarily effective for lowering elevated triglyceride levels, but are not approved by the Food and Drug Administration for routine use in lowering cholesterol levels.

After starting drug therapy, the LDL-cholesterol level should be measured at four to six weeks, and then again at three months. If the response to drug therapy is adequate (ie, the LDL-cholesterol goal has been achieved), then the patient should be seen every four months, or more frequently when drugs requiring closer followup are used, in order to monitor the cholesterol response and possible side effects of therapy. For long-term monitoring, serum total cholesterol alone can be measured at most follow-up visits, with lipoprotein analysis (and LDL-cholesterol estimation) carried out once a year.

If the response to initial drug therapy is not adequate, the patient should be switched to another drug, or to a combination of two drugs. The combination of a bile acid sequestrant with either nicotinic acid or an HMG CoA reductase inhibitor has the potential of lowering LDL-cholesterol levels by 40% to 50% or more. The combination of colestipol and nicotinic acid has been shown to beneficially influence coronary atherosclerotic lesions. For most patients, the judicious use of one or two drugs should be

able to provide an adequate LDL-cholesterol–lowering effect.

Drug therapy is likely to continue for many years, or for a lifetime. Hence, the decision to add drug therapy to the regimen should be made only after vigorous efforts at dietary treatment have not proven sufficient. The patient must be well informed about the goals and side effects of medication and the need for long-term commitment. In the ideal treatment setting, the management of high-risk cholesterol levels would call on the expertise of a variety of professionals. The office nurse or physician's assistant can help greatly in promoting adherence to dietary and drug therapy. A registered dietitian can be of great value in dietary therapy. The pharmacist can help to provide counseling and promote adherence with drug therapy. Consultation with a lipid specialist is useful for patients with unusually severe, complex, or refractory lipid disorders.

CLASSIFICATION, PREVALENCE, DETECTION, AND EVALUATION

Background and Introduction

This report provides practical guidelines for clinicians to use in measuring and reducing blood cholesterol in adult patients. (This report addresses patients 20 years of age and above; a separate panel will provide guidelines for children and adolescents.) The report adds a more specific set of recommendations to basic policies set forth by previous bodies, notably the National Institutes of Health (NIH) Consensus Development Conference on Lowering Blood Cholesterol to Prevent Heart Disease.[1] While it is recognized that approaches for modifying the cholesterol levels in whole population groups are important, this report focuses on caring for individual patients.

Basic Description of Lipids and Lipoproteins.—Cholesterol is a fatlike substance (lipid) that is a key component of cell membranes and a precursor of bile acids and steroid hormones. Cholesterol travels in the circulation in spherical particles containing both lipids and proteins called lipoproteins. The cholesterol level in blood plasma is determined partly by inheritance and partly by the fat and cholesterol content of the diet. Other factors such as obesity and physical inactivity may also play a role.

Three major classes of lipoproteins can be measured in the serum of a fasting individual: very low density lipoproteins (VLDL), LDL, and HDL. The LDL are the major atherogenic class, and, typically, contain 60% to 70% of the total serum cholesterol. The HDL usually contain 20% to 30% of the total cholesterol, and their levels are inversely correlated with risk for CHD. The VLDL, which are largely composed of triglycerides, contain 10% to 15% of the total serum cholesterol.

Because most of the cholesterol in the serum is found in the LDL, the concentration of total cholesterol is closely correlated with the concentration of LDL-cholesterol. Thus, while LDL-cholesterol is the actual target of cholesterol-lowering efforts, total cholesterol can be used in its place in the initial stages of evaluating a patient's serum lipids. Testing for serum total cholesterol is more available and less expensive and does not require that the patient be fasting. On the other hand, LDL-cholesterol offers more precision as a risk factor and is therefore preferred for clinical decisions about interventions to lower blood cholesterol, especially in patients who may be candidates for cholesterol-lowering drugs.

Rationale for Intervention.—*The Evidence That LDL-Cholesterol Is a Cause of CHD.*—The conclusion that high levels of LDL-cholesterol are a cause of coronary atherosclerosis and produce an increased risk of CHD comes from the congruent results of many studies.

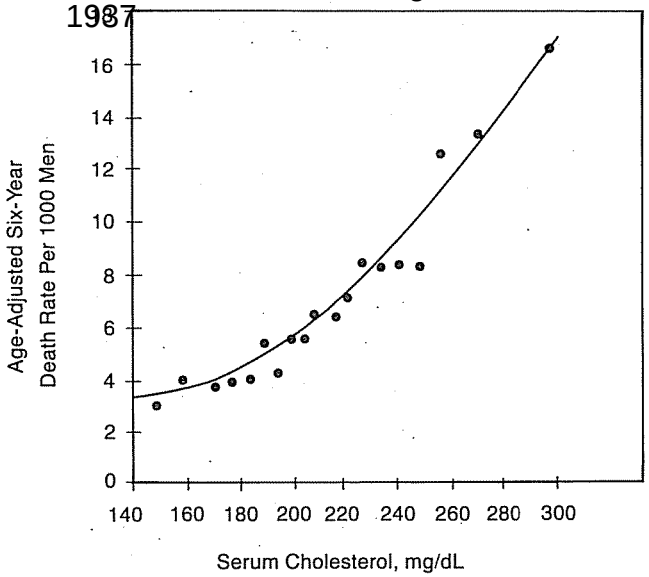

Fig 1.—Relationship of serum cholesterol to coronary heart disease (CHD) death in 361 662 men 35 to 57 years of age during an average followup of six years. Each point represents median value for 5% of the population.[5] Key points are as follows: (1) risk increases steadily, particularly above levels of 200 mg/dL; and (2) the magnitude of the increased risk is large, fourfold in the top 10% as compared with the bottom 10%.

Epidemiologic Evidence.—A large body of epidemiologic evidence supports a direct relationship between the level of serum total and LDL-cholesterol and the rate of CHD.[2-4] Comparisons among various populations throughout the world reveal a direct correlation between serum cholesterol levels and CHD rates. People who have migrated to a country that has a higher average serum cholesterol level gradually acquire the dietary habits, serum cholesterol level, and CHD rates of their new country. Prospective studies of the individuals within a population have uniformly shown that serum cholesterol levels predict the future occurrence of CHD morbidity and mortality. This association is continuous throughout the range of cholesterol levels in the population (Fig 1).[5,6] At higher levels of serum cholesterol, the relationship becomes particularly strong. For persons with cholesterol values in the top 10% of the population distribution, the risk of CHD mortality is four times as high as the risk in the bottom 10% of the population.

Genetic and Physiologic Evidence.—Premature CHD can result from high LDL-cholesterol levels even in the absence of any other risk factors.[7] This is most clearly demonstrated in children who have the rare homozygous familial hypercholesterolemia, a disorder characterized by the absence of the specific cell-surface receptors that normally remove LDL from the circulation.[8] The LDL-cholesterol levels can be as high as 1000 mg/dL, and severe atherosclerosis and CHD can develop during the first two decades of life. Patients with the more common heterozygous form of familial hypercholesterolemia and partial deficiencies of LDL-receptor function commonly develop premature CHD in the middle decades of life.

Animal Model Evidence.—Animal models have demonstrated important relationships between LDL-cholesterol and atherosclerosis.[9] Many animal species (including monkeys and baboons) develop atherosclerosis when fed

diets that raise their serum cholesterol levels. These hypercholesterolemic animals develop intimal lesions that progress from fatty streaks to complicated ulcerated plaques resembling those of human atherosclerosis. Severe atherosclerosis in monkeys regresses when the blood cholesterol is lowered substantially for an extended period by diet or drugs. These studies thus support a causal relationship between LDL-cholesterol and atherosclerosis, and suggest that this process may be reversible under some circumstances.

The Evidence That Reducing LDL-Cholesterol Levels Will Prevent CHD.—The evidence noted above from epidemiologic, genetic, and animal investigations strongly supports a causal link between elevated serum cholesterol levels and CHD. In addition, clinical trials have shown that this risk can be altered—that lowering LDL-cholesterol in men with high levels decreases the incidence of CHD.

The issue of whether lowering LDL-cholesterol levels by dietary and drug interventions can reduce the incidence of CHD has been addressed in more than a dozen randomized clinical trials. One of the largest, the Coronary Primary Prevention Trial, which compared the cholesterol-lowering drug cholestyramine with a placebo, produced statistically significant reductions in LDL-cholesterol levels and in the incidence of CHD.[10] An aggregate analysis that pools the results of serum cholesterol-lowering trials confirms an effect on CHD incidence. Moreover, the Coronary Drug Project has shown a significant decrease in overall mortality (compared with the placebo group) in a long-term followup of men treated with nicotinic acid after myocardial infarction.[11] In addition, a recent angiographic study showed that cholesterol-lowering dietary and drug therapy slowed the progression and produced regression of coronary atherosclerosis in men with bypass grafts.[12]

In summary, these findings support the conclusion that lowering total and LDL-cholesterol levels will reduce the subsequent incidence of CHD events. Moreover, the pooled analysis of clinical trial findings suggests that intervention is as effective in secondary prevention (preventing recurrent myocardial infarction and death in patients who have had a heart attack) as it is in primary prevention. The direct evidence from clinical trials is strongest in middle-aged men with high initial cholesterol levels. However, the complete set of evidence, including the epidemiologic observations and animal experiments, strongly supports the generalization that reducing total and LDL-cholesterol levels is also likely to reduce CHD incidence in younger and older men, in women, and in individuals with more moderate elevations of cholesterol.

The Magnitude of the Reduction in CHD.—Epidemiologic studies and clinical trials are remarkably consistent in supporting the projection that for individuals with serum cholesterol levels initially in the 250 to 300 mg/dL range, each 1% reduction in serum cholesterol level yields approximately a 2% reduction in CHD rates.[13] Thus, for example, it is reasonable to estimate that a 10% to 15% reduction in serum cholesterol level resulting from the diets recommended in this report should reduce CHD risk by 20% to 30%.

The *absolute magnitude* of these benefits will probably be greatest in patients who are at high risk because of the presence of other risk factors, such as cigarette smoking and hypertension. This concept is illustrated in Table 3 using data from the Multiple Risk Factor Intervention Trial (MRFIT). Among nonsmokers with normal blood pressure, the risk of CHD death per 1000 men in the six years of observation was 6.4 in the top quintile of serum cholesterol and 1.6 in the bottom quintile, a difference of 4.8. Among smokers with hypertension, the comparable figures were 21.4 and 6.3, a difference of 15.1. Thus, an intervention that lowered cholesterol levels from the highest to the lowest quintile should have three times the benefit (15 vs five deaths prevented per thousand persons) when applied to men who have the other two risk factors (assuming no change in those other risk factors). These risk relationships are the basis for recommending lower cholesterol cutpoints and goals for treating patients who, for other reasons (in addition to cholesterol), are at high risk for developing CHD.

Table 3.—Coronary Heart Disease Deaths per 1000 in Men 35 to 57 Years of Age With an Average Followup of Six Years According to Serum Cholesterol Quintile and Presence or Absence of Other Risk Factors.[14] The Difference in Absolute Risk in the Highest vs the Lowest Quintile of Serum Cholesterol Is Greater in Patients Who Are at High Risk for Other Reasons.

Serum Cholesterol Quintile, mg/dL	Normotensive Nonsmoker	Hypertensive Smoker
<182	1.6	6.3
182 to 202	2.5	10.0
203 to 220	2.7	15.5
221 to 244	3.8	16.6
≥245	6.4	21.4

Classification of Patients by Total and LDL-Cholesterol Levels.—Population distributions for serum total cholesterol and LDL-cholesterol levels in the United States are provided in Appendix I, Tables. To convert serum values to plasma, multiply by 0.97. To convert cholesterol values in milligrams per deciliter to millimoles per liter, multiply by 0.02586. To convert triglyceride values in milligrams per deciliter to millimoles per liter, multiply by 0.01129.

The classification system (Fig 2) begins with measurement of the total cholesterol level. Serum is most frequently used for this measurement, and cholesterol levels in this report are stated as serum values. (Cholesterol levels can also be measured on plasma. If, as is customary, ethylenediaminetetraacetic acid [EDTA] is used as an anticoagulant, the results should be multiplied by 1.03 to arrive at the serum equivalent.) Levels below 200 mg/dL are classified as "desirable blood cholesterol," those 200 to 239 mg/dL as "borderline-high blood cholesterol," and those 240 mg/dL and above (corresponding to approximately the top 25% of the entire adult population 20 years of age and above) as "high blood cholesterol."

Patients with high blood cholesterol need additional evaluation and are further classified for the purposes of clinical decisions about possible dietary and drug treatment by performing lipoprotein analysis and estimating the more specific determinant of CHD risk, the LDL-cholesterol level. Levels of LDL-cholesterol that are 160 mg/dL and above are classified as "high-risk LDL-cholesterol."

Because the relationship between serum cholesterol level and CHD is a continuous and steadily increasing one (Fig 1), these cutpoints are necessarily somewhat arbitrary. However, this is also true of other risk factors, such as blood pressure, and the success of basing clinical decisions on whether or not a patient is classified as hypertensive indicates the value of establishing cutpoints for clinical decisions. The 240 mg/dL cutpoint for total serum cholesterol is a level at which CHD risk is almost double that at 200 mg/dL, and is rising steeply. Patients with cholesterol levels at or above this cutpoint have sufficiently high risk

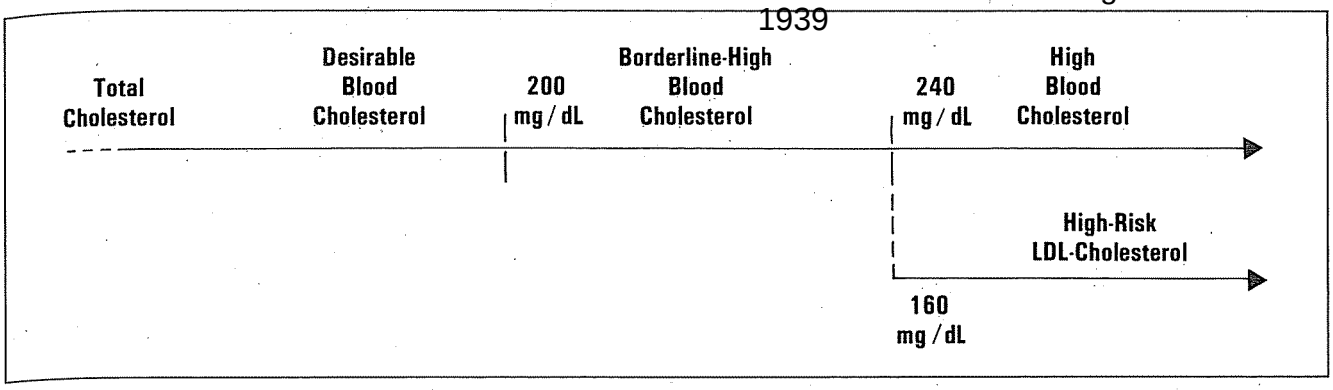

Fig 2.—Classification by total and low density lipoprotein (LDL)–cholesterol levels. Key points are as follows: (1) serum cholesterol is used for initial classification; (2) low density lipoprotein–cholesterol is used for those with high levels.

to warrant more detailed evaluation and possible treatment.

Other Risk Factors for CHD.—Coronary heart disease is a disease of multifactorial etiology, and other risk factors should also be considered in preventive medical efforts. These include modifiable factors like hypertension and cigarette smoking, which are appropriate targets for intervention efforts. (Assistance in intervention efforts aimed at hypertension and cigarette smoking may be obtained from two National Heart, Lung, and Blood Institute publications: "The 1984 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure" [to be updated in 1988]; and "Clinical Opportunities for Smoking Intervention—A Guide for the Busy Physician.") Everyone tested for blood cholesterol should also be examined for other risk factors (Table 4), and intervention should be undertaken as appropriate. All patients should receive educational materials that describe general dietary and life-style approaches to reducing the risk of CHD. (These materials may be obtained from a variety of sources—see the list in the National Cholesterol Education Program publication "Cholesterol Resources for the Physician.") Advice to quit smoking is particularly important because it has the potential not only to reduce CHD risk by 50%, but also to prevent cancer and chronic lung disease.

In addition to being candidates for intervention, these modifiable factors increase the absolute level of CHD risk and thereby enhance the potential value of reducing cholesterol levels. This is also true for the fixed risk factors like older age, male sex, family history of premature CHD, and CHD in the patient. Two other lipid and lipoprotein factors that have a bearing on CHD, HDL-cholesterol and triglyceride, are not dealt with in this report as direct targets for intervention but enter into clinical decisions in ways that are discussed in the sections that follow and in Appendix II.

The Patient-Based Approach and the Population-Based Approach.—The 1984 Consensus Conference and other groups have recommended two major strategies for preventing CHD by lowering blood cholesterol levels.[1,13-15] One is the subject of this report: a patient-based approach that seeks to identify individuals at high risk who will benefit from intensive intervention efforts. The goal here is to establish total and LDL-cholesterol cutpoints that define the candidates for medical intervention, and to provide guidelines on how to detect, set goals for, treat, and monitor these patients over time.

The other strategy is the population-based approach that seeks to lower the mean serum cholesterol level by modifying the dietary habits of the entire population. This strategy has the general goal of lowering the serum cholesterol levels of the population at large.

These two strategies are complementary, not competitive, and the National Cholesterol Education Program is considering both in the development of its activities. This report is the product of an expert panel focused on the patient-based approach. Another panel is charged with examining the scientific evidence and making recommendations for the population-based approach.

The Importance of a Multidisciplinary Team Approach.—This report presents guidelines for interventions that are partly the responsibility of the physicians, dietitians, nurses, pharmacists, and other health professionals who must work together as a team to decide on the best approach for testing and treating each patient, and for implementing and following up these recommendations. The interventions are also the responsibility of the patient, for whom the challenge is to make the dietary and other life-style changes that are needed for successful reduction of CHD risk.

Table 4.—Risk Status Based on Presence of CHD Risk Factors Other Than LDL–Cholesterol

The patient is considered to have a high risk status if he or she has one of the following:
Definite CHD: the characteristic clinical picture and objective laboratory findings of either:
Definite prior myocardial infarction, or
Definite myocardial ischemia, such as angina pectoris
Two other CHD risk factors:
Male sex*
Family history of premature CHD (definite myocardial infarction or sudden death before 55 years of age in a parent or sibling)
Cigarette smoking (currently smokes more than ten cigarettes per day)
Hypertension
Low HDL–cholesterol concentration (below 35 mg/dL confirmed by repeated measurement)
Diabetes mellitus
History of definite cerebrovascular or occlusive peripheral vascular disease
Severe obesity (≥30% overweight)

*Male sex is considered a risk factor in this scheme because the rates of CHD are three to four times higher in men than in women in the middle decades of life and roughly two times higher in the elderly. Hence, a man with one other CHD risk factor is considered to have a high-risk status, whereas a woman is not so considered unless she has two other CHD risk factors.

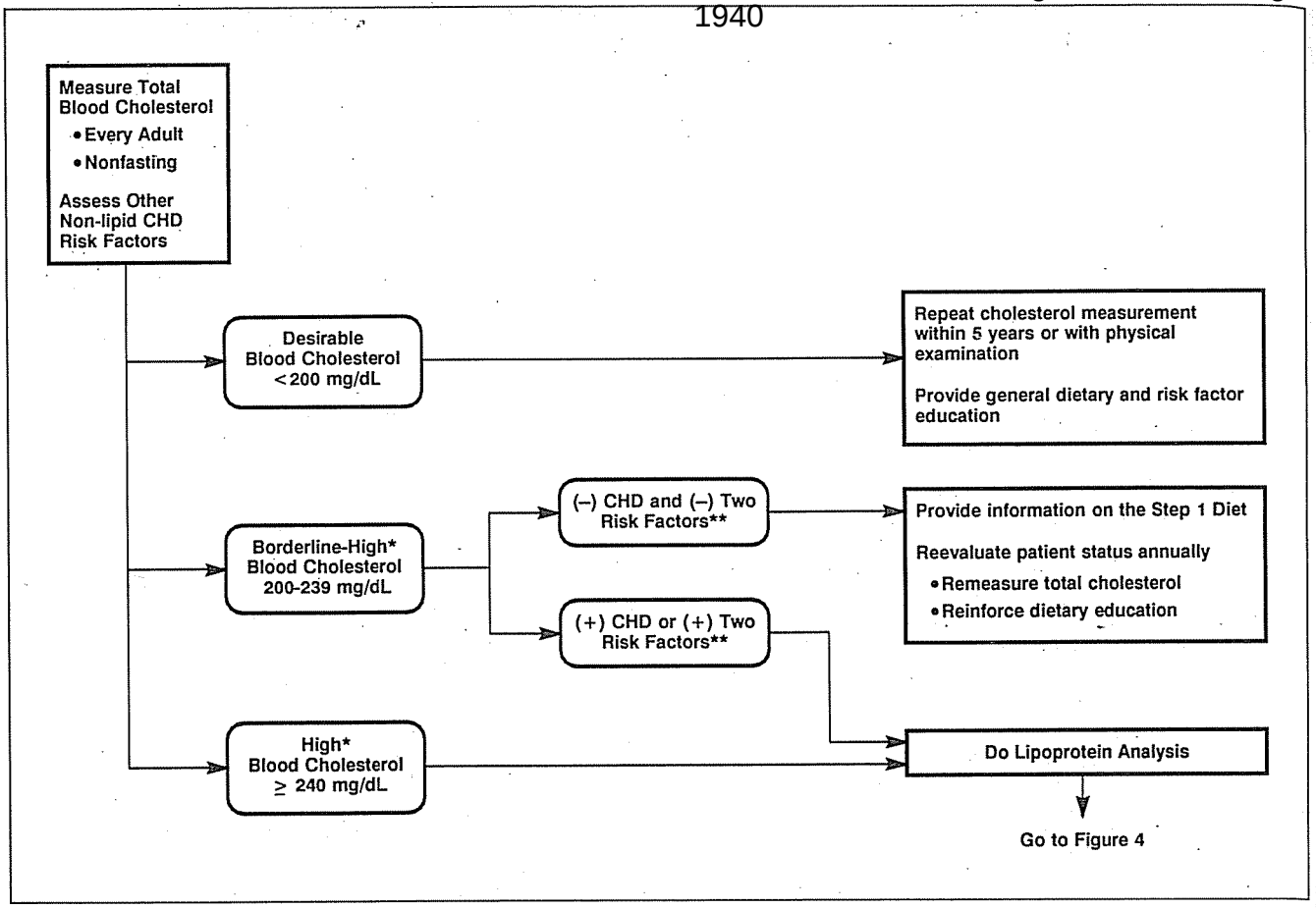

Fig 3.—Initial classification based on total cholesterol. CHD indicates coronary heart disease; asterisk, must be confirmed by obtaining repeated measurements and then using the average value; double asterisks, one of which can be male sex (Table 4).

Detection and Evaluation

Who Should Be Tested.—The total cholesterol level should be measured in all adults 20 years of age and over at least once every five years. Although screening programs that have the specific purpose of inviting the public to receive this test can be used (provided that care is taken to assure that the screening determination is accurate and that there is appropriate followup for further tests and treatment), the usual approach is through case finding. Case finding is defined as testing the cholesterol level as part of any medical examination.

Classification of Patients.—*Initial Classification Based on Total Cholesterol Level.*—The schedule for evaluation and followup of serum cholesterol concentration is shown in Fig 3. The schedule begins with measurement of the nonfasting serum total cholesterol level and an assessment of other nonlipid risk factors including blood pressure, smoking, and history of CHD in the patient or of premature CHD in family members. The presence of a high cholesterol level is confirmed with a second test and then the fasting LDL-cholesterol level is measured in order to provide a more precise estimate of risk on which to base treatment. Patients should be asked not to change their eating habits during this series of baseline tests.

Patients with a *desirable blood cholesterol* level at this initial test (<200 mg/dL) should be given advice and educational materials on the diet recommended for the general population and advised to have another serum cholesterol test within five years. As with all patients, these individuals should also have been evaluated for hypertension, cigarette smoking, and other risk factors, and should be given other forms of preventive medical care as appropriate.

Patients with a serum cholesterol level of 200 mg/dL or greater should have the measurement repeated in one to eight weeks. If the level is within 30 mg/dL of the first result, the average of the two values can be used to guide subsequent decisions; otherwise, a third test should be obtained within another one to eight weeks, and the average of the three values used. Getting more than one cholesterol measurement at the outset of treatment is extremely important to assess the patient's serum cholesterol status accurately, because cholesterol levels can fluctuate considerably from day to day in a given individual. (The standard deviation of repeated measurements in an individual over time has been reported as 18 mg/dL for total cholesterol[16] and 15 mg/dL for LDL-cholesterol.[17])

Most patients with *borderline–high blood cholesterol* levels (200 to 239 mg/dL) confirmed by two or more readings are given dietary education designed to lower their serum cholesterol level and are followed up annually. However, those individuals in the 200-239 mg/dL range who have definite CHD or two other nonlipid CHD risk factors (as defined in Table 4) should have lipoprotein analysis and their LDL-cholesterol level determined.

All patients with *high blood cholesterol* levels (240 mg/dL or greater), as well as those with levels from 200 to 239 mg/dL who have definite CHD or two other

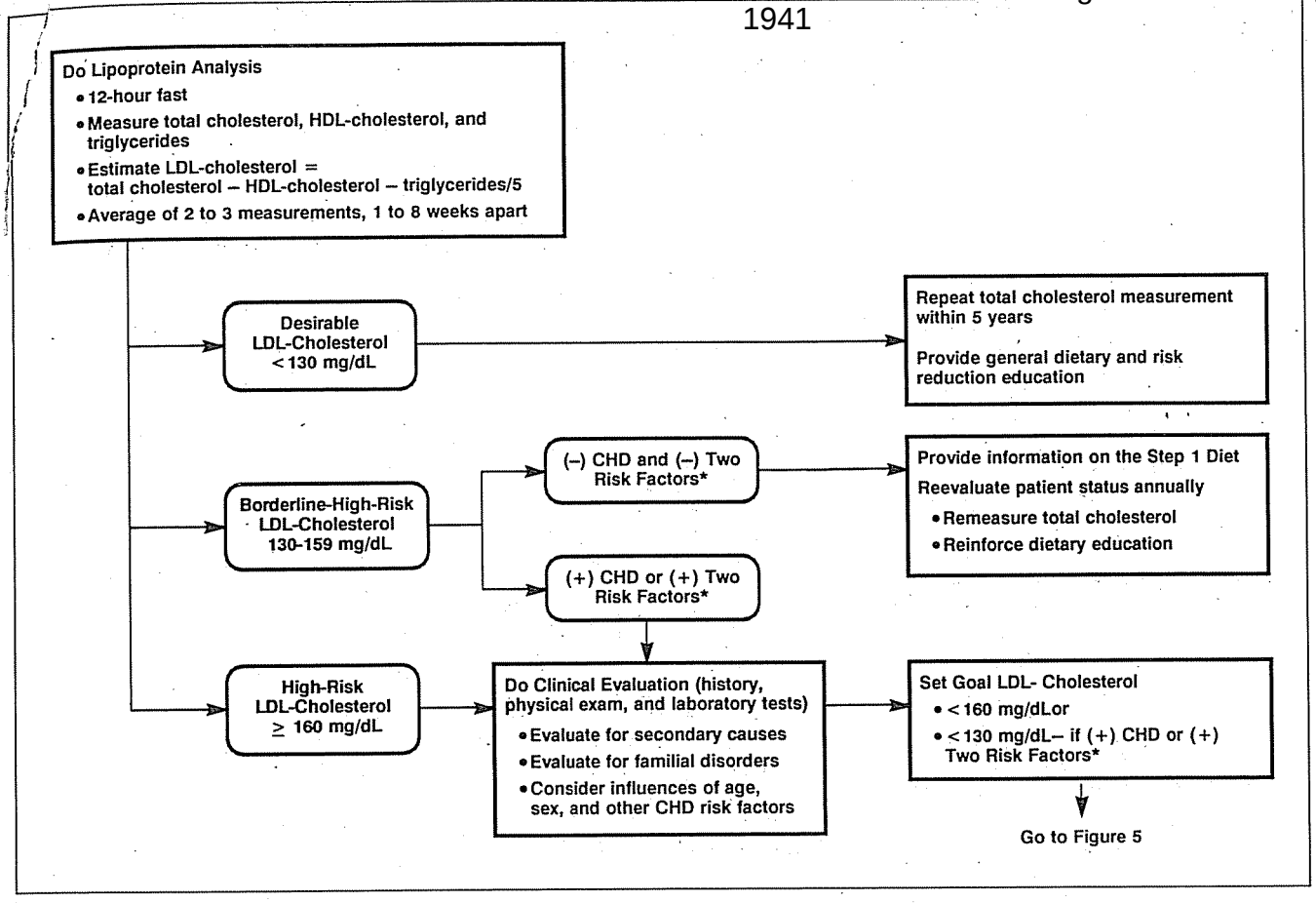

Fig 4.—Classification based on low density lipoprotein (LDL)–cholesterol. Asterisk indicates one of which can be male sex (Table 4); CHD, coronary heart disease; HDL, high density lipoprotein.

CHD risk factors (Table 4), should be tested for the serum level of LDL-cholesterol.

Subsequent Classification Based on LDL-Cholesterol Level.—The action scheme based on LDL-cholesterol level is shown in Fig 4. Two measurements of LDL-cholesterol after an overnight fast are made one to eight weeks apart, and the average is used for clinical decisions unless the two values differ by more than 30 mg/dL (in which case a third test is carried out, and the average of all three is used). The repeated testing of LDL-cholesterol is important for the same reasons given earlier for total cholesterol—the variability of the level from day to day, and the importance of establishing an accurate baseline on which to design the best treatment program. It is possible, however, to save time and effort by making the first LDL-cholesterol measurement on the same specimen that is used for the second test of total cholesterol; this is an especially attractive option for patients with very high levels of total cholesterol (above 260 mg/dL) on the first test.

The LDL-cholesterol levels are classified on the basis of average values as *desirable* (below 130 mg/dL), *borderline-high-risk* (130 to 159 mg/dL), or *high-risk* (160 mg/dL or greater). Patients with desirable LDL-cholesterol fall into the same class as those with desirable total cholesterol levels (<200 mg/dL), and are given general educational materials and tested again within five years. Those with borderline-high-risk LDL-cholesterol (130 to 159 mg/dL) are given information about and advised to follow a fat-modified diet; they are reevaluated annually unless they have definite CHD or two other risk factors (one of which can be male sex [Table 4]). Such patients (with borderline-high-risk LDL-cholesterol who do have CHD or two other risk factors), together with all patients in the high-risk LDL-cholesterol group (≥160 mg/dL), are clinically evaluated as described below, and then enter a cholesterol-lowering treatment program.

Methods of Detection.—Serum *total cholesterol* levels can be measured at any time of day in the nonfasting state, since total cholesterol concentrations do not change appreciably after a fat-containing meal. Patients should be following their ordinary eating habits and be in their usual state of health. Patients who are acutely ill, are losing weight, are pregnant, or have had a myocardial infarction within the past three months should be rescheduled; the cholesterol levels obtained in such patients may not be representative of their usual levels. To prevent an effect of posture or stasis on the cholesterol determination, venipuncture should be carried out on patients who have been in the sitting position for at least five minutes, and the tourniquet should be used for as brief a period as possible. The blood may be collected either as serum (no anticoagulant) or as plasma (in EDTA). If blood is obtained without anticoagulant, it should be allowed to clot for 30 minutes at room temperature, and the clot should be detached from the wall of the tube prior to centrifuging. Rapid capillary blood (fingerstick) methodology for cholesterol measurement is currently under development and evaluation. Should this methodology prove reliable, it could be suitable

for initial cholesterol determinations.

Low density lipoprotein–cholesterol determinations can also be carried out on either serum or plasma, provided that, as with total cholesterol measurements, plasma values are multiplied by 1.03 to correct them to the serum cutpoints specified in this report. However, because the LDL-cholesterol value is estimated from measurements of other lipids, including triglyceride, blood samples should be collected from patients who have fasted for at least 12 hours (except for water or black coffee).

The LDL-cholesterol level is estimated from measurements of the levels of total cholesterol, total triglycerides, and HDL-cholesterol. If the triglyceride value is below 400 mg/dL, then this value can be divided by five to estimate the VLDL-cholesterol level. Since total cholesterol is the sum of LDL-cholesterol, HDL-cholesterol, and VLDL-cholesterol, LDL-cholesterol can be calculated as follows (all quantities are in milligrams per deciliter): LDL-Cholesterol = Total Cholesterol − HDL-Cholesterol − (Triglyceride/5).[18] (A recent report suggests that, in this formula, dividing the triglyceride value by 6, rather than 5, may provide a more accurate estimation of the LDL-cholesterol level.[19] Further studies may validate the use of triglyceride/6 as the preferred way of estimating LDL-cholesterol.) If the triglyceride value is above 400 mg/dL, LDL-cholesterol estimation by the above formula becomes less accurate. For such patients, ultracentrifugation in a specialized laboratory can be used to give a more accurate LDL-cholesterol level; it may be appropriate to refer such patients to a lipid specialist.

The choice of laboratory is an important issue because there is considerable variability in the accuracy with which laboratories measure cholesterol. This measurement variability is another reason for recommending that more than one cholesterol measurement be obtained and average values be used at key decision points in this report. All recommendations about cholesterol levels in this report presuppose accurate and reliable measurements. The physician should seek a laboratory that participates in a suitable standardization program. The issue of laboratory methods and their standardization is being addressed by the Laboratory Standardization Panel of the National Cholesterol Education Program.

Clinical Evaluation.—All patients with an LDL-cholesterol level ≥160 mg/dL, and those with a level of 130 to 159 mg/dL and high risk status, as defined in Table 4, should be evaluated clinically. They should then be assigned a goal LDL-cholesterol level and enter the program for cholesterol-lowering treatment.

The clinical evaluation, which includes a history, physical examination, and basic laboratory tests, has three aims. The first is to determine whether the high LDL-cholesterol level is caused by another disease or by a drug. The second is to determine whether a genetic disorder may underlie the elevated LDL-cholesterol. The third aim is to ensure that the patient is fully characterized with regard to age, sex, and the presence or absence of definite CHD and of other CHD risk factors, in order to use this information in decisions about treatment directed at LDL-cholesterol.

Secondary High Blood Cholesterol.—The clinical evaluation for secondary (and possibly reversible) forms of high-risk LDL-cholesterol includes consideration of, and, where appropriate, ruling out, the following conditions: hypothyroidism; nephrotic syndrome; diabetes mellitus; obstructive liver disease; and drugs that may raise LDL-cholesterol levels, particularly progestins and anabolic steroids. High blood cholesterol secondary to other diseases or drugs can be detected by clinical evaluation and, when indicated, by the following laboratory tests: urinalysis, complete blood cell count, and serum thyroid-stimulating hormone (TSH), glucose, alkaline phosphatase, and albumin. When one of the causes of secondary high cholesterol is present, the usual approach is to treat the disease or discontinue the drug (if possible) and then to reevaluate the LDL-cholesterol level.

Familial Disorders.—In most cases, high blood cholesterol is not secondary to some other condition, and the patient has a primary form of LDL-cholesterol elevation. This can be either genetic (familial) or sporadic (often diet induced), and the next step is to consider which of these possibilities is more likely. Diagnosing genetic disorders helps clarify the etiology and management of LDL-cholesterol elevations in affected patients, and emphasizes the desirability of measuring cholesterol in first-degree relatives (parents, siblings, children) in order to identify those who may need cholesterol-lowering treatment.

The genetic hyperlipidemias are described in Appendix II; two important ones are summarized here. One of these is familial hypercholesterolemia (FH), an autosomal dominant disorder of the LDL receptor. Heterozygotes with this disorder have a population frequency of about one in 500 and often have serum cholesterol levels greater than 300 mg/dL, tendon xanthomas, and premature CHD. Another important genetic cause of high-risk LDL-cholesterol levels is familial combined hyperlipidemia (FCHL). Affected family members may have high serum levels of LDL-cholesterol, or of triglyceride, or both. Such patients generally do not have tendon xanthomas, but premature CHD is common. The prevalence of these two familial disorders among survivors of myocardial infarction under 60 years of age is 5% for FH and 15% for FCHL.[20]

Other Lipid Risk Factors.—The level of plasma HDL-cholesterol is inversely related to CHD rates in most epidemiologic studies even after adjustment for the influence of other risk factors (see Appendix II). Although there is no direct experimental evidence that raising HDL-cholesterol levels reduces the risk of CHD, the life-style interventions that raise the level of this lipoprotein—quitting smoking, reducing obesity, and exercising—are good advice for other reasons and should be recommended to all patients regardless of their HDL-cholesterol levels. One other life-style approach to increasing the level of HDL-cholesterol—increasing the intake of alcohol—is not recommended because of the possibility of encouraging excessive intake. The issue of low HDL-cholesterol and its management is discussed further in Appendix II.

Reliance on a ratio of either total or LDL-cholesterol to HDL-cholesterol as a key factor in decisions regarding treatment is not a practice recommended in this report. Blood pressure and smoking are not combined into a single number because the clinician needs to know both facts separately in order to recommend an intervention. Similarly, HDL-cholesterol and LDL-cholesterol are independent risk factors with different determinants, and combining them into a single number conceals information that may be useful to the clinician. The HDL-cholesterol level does, however, contribute to decisions about treatment for LDL-cholesterol, because a low level increases the CHD risk of the patient (Table 4).

The level of plasma triglyceride is also a risk factor for CHD in most epidemiologic studies. In general, however, it is not an independent risk factor, ie, the association usually disappears when statistically adjusted for plasma total cholesterol and HDL-cholesterol levels. In the Framingham Study, however, the plasma triglyceride level was found to be an independent predictor of CHD risk in

women.[21] The recommended approach to the problem of hypertriglyceridemia is described in the report of the National Institutes of Health Consensus Development Conference on Treatment of Hypertriglyceridemia,[22] and is summarized in Appendix II. In the absence of pathophysiologic or animal evidence that triglyceride is atherogenic or that lowering the plasma level lowers the risk of CHD, intervention specifically directed at this lipid (except in the rare patient with a very high level that may cause pancreatitis) is not generally recommended at this time. On the other hand, many individuals with elevated triglyceride levels have associated low levels of HDL-cholesterol and/or high levels of LDL-cholesterol, which do influence decisions about intervention to reduce the risk of CHD in ways described in this report. Moreover, hypertriglyceridemia alone may be a marker for familial combined hyperlipidemia, which warrants therapy to prevent CHD.

Other Major (Nonlipid) Risk Factors.—Information on whether CHD or its other risk factors are present is used to assess whether the patient has reasons unrelated to LDL-cholesterol for being at high risk of a CHD event or death. The search is important because modifiable risk factors such as hypertension and cigarette smoking are themselves important targets for intervention. In addition, the presence of any risk factor, whether modifiable or not, influences clinical decisions about LDL-cholesterol because the increased absolute level of risk may increase the potential benefit from lowering the level of LDL-cholesterol (Table 3).

This principle can be used in a general way by the clinician, and also as a specific rule in the decision schemes set out in Figs 3 and 4. In Fig 4 the presence of high risk status due to factors other than LDL-cholesterol establishes a lower cutpoint for triggering intervention and a lower therapeutic goal for LDL-cholesterol. The definitions of high-risk status are given in Table 4. Because the presence of CHD is by far the strongest factor that influences the risk of recurrent CHD events or death, it is particularly important in clinical decisions for treating LDL-cholesterol. Thus, this report emphasizes the importance of both primary and secondary prevention.

Race, Sex, and Age.—The percentage of adults with high blood cholesterol by age, race, and sex is given in Table 5. The prevalence rises with age to plateau at about 50 years of age, and does not vary appreciably by race or sex except for the higher prevalence in older women. (This high prevalence in older women is due to the fact that they have high levels of both LDL- and HDL-cholesterol.) Additional information on the distributions of total and LDL-cholesterol levels in the population is given in Appendix I. This section addresses the CHD risk in different groups, with the implications for managing LDL-cholesterol.

RACE.—Race is not included in Table 4 because available evidence suggests that the clinical management of LDL-cholesterol should not differ according to race in the United States. (This report is not specifically directed at populations in other countries, but the guidelines would probably apply reasonably well to any country where CHD is endemic at similar levels to those in the United States.)

SEX.—Sex, on the other hand, should be considered as a risk factor, as described in Table 4, when determining the risk status of an individual patient. In women as in men, CHD is the major cause of death, and cholesterol levels are predictive of CHD. However, the rates of CHD are three to four times higher in men than in women in the middle decades of life and roughly two times higher in the elderly.[24,25] Hence, the absolute magnitude of the potential benefit from lowering blood cholesterol in general, and the benefit/risk ratio of drug therapy in particular, is greater for men than for women. Thus, male sex is considered a risk factor in decisions about the cutpoints and goals of cholesterol-lowering treatment.

Table 5.—US Prevalence of High Blood Cholesterol* by Age, Race, and Sex (Percent of Each Population)[23]

	Men		Women	
Age, y	White	Black	White	Black
20-74	25.0	23.9	29.2	23.7
20-24	6.1	2.9	6.5	7.0
25-34	15.0	19.3	12.4	8.7
35-44	27.9	24.5	21.1	16.9
45-54	36.5	40.3	40.6	40.7
55-64	37.3	35.3	53.7	46.5
65-74	32.4	27.2	52.1	48.4

*Serum concentration of cholesterol ≥240 mg/dL.

AGE.—Age is a complicated factor to consider. Beginning at 20 years of age, the mean total and LDL-cholesterol levels increase by about 40 mg/dL during the next two to three decades; in the elderly, the levels decline slightly (see Appendix I for age-specific data). Two major LDL-cholesterol cutpoints are recommended in this report: 160 mg/dL identifies the group with high-risk LDL-cholesterol, and (as discussed later in the section on drug treatment) 190 mg/dL identifies the group with "very-high-risk" LDL-cholesterol for whom consideration of drug therapy is warranted even in the absence of other risk factors. These cutpoints approximate the 75th and 90th percentiles for 35- to 60-year-old patients. Using these same cutpoints in younger patients will have the effect of designating a smaller proportion of the younger population as being in the high-risk categories.

The strategy recommended by the Cholesterol Consensus Conference for making clinical decisions about patients 20 to 39 years of age is to use cutpoints that correspond to the age-specific 75th and 90th percentile values (Appendix I). Using the Consensus Conference recommendations concerning the 75th percentile values, adults 20 to 29 years of age would be considered (in the terminology of the present report) to have high blood cholesterol for levels exceeding 200 mg/dL; those 30 to 39 years of age would be in this category if total cholesterol exceeded 220 mg/dL. Giving dietary treatment to the top 25% of the young adult population is probably desirable in order to prevent the development of atherosclerosis at an earlier stage in the disease. Recommending drug treatment to as large a group as the top 10% of young adults, however, is premature until additional evidence becomes available on the safety of using lipid-lowering drugs for many decades. There is, moreover, the important fact that age is a very strong risk factor, and therefore the absolute magnitude of the benefit (and the benefit/risk ratio) increases with age for the reasons given earlier.

Patients 60 years of age and above are another issue. There is little direct clinical trial evidence on whether elderly patients will benefit from intervention, and the strength of the association between LDL-cholesterol and CHD diminishes with age. However, LDL-cholesterol does continue to have some association with CHD, and the clinical trial evidence for the effectiveness of intervention after myocardial infarction suggests that lowering LDL-cholesterol is beneficial even in patients who already have

Table 6.—Dietary Therapy of High Blood Cholesterol Level

Nutrient	Recommended Intake	
	Step-One Diet	Step-Two Diet
Total fat	Less than 30% of total calories	Less than 30% of total calories
Saturated fatty acids	Less than 10% of total calories	Less than 7% of total calories
Polyunsaturated fatty acids	Up to 10% of total calories	Up to 10% of total calories
Monounsaturated fatty acids	10% to 15% of total calories	10% to 15% of total calories
Carbohydrates	50% to 60% of total calories	50% to 60% of total calories
Protein	10% to 20% of total calories	10% to 20% of total calories
Cholesterol	Less than 300 mg/d	Less than 200 mg/d
Total calories	To achieve and maintain desirable weight	To achieve and maintain desirable weight

advanced disease. Moreover, the fact that age is associated with a high risk of CHD in the later decades of life means that the absolute magnitude of the potential benefits of intervention remains substantial in the elderly.[25]

Summarizing the issue of sex and age, the recommendations and cutpoints in this report are meant to apply to all adults 20 years of age and above. There is room, however, for modifications based on the judgment of the physician and the preferences of the patient when dealing with individual patients, particularly young adults, the elderly, and women.

DIETARY TREATMENT

Cutpoints and Goals for Dietary Therapy

Patients with high-risk LDL-cholesterol levels (≥160 mg/dL), and those with borderline-high-risk LDL-cholesterol (130 to 159 mg/dL) who also have definite CHD or two other risk factors (Table 4), should enter a program of dietary therapy instituted by the physician. The *minimal* goals of therapy are as follows: (1) to lower LDL-cholesterol to below 160 mg/dL if the patient has neither definite CHD nor two other CHD risk factors (Table 4); or (2) to lower LDL-cholesterol to below 130 mg/dL if definite CHD or two other CHD risk factors (Table 4) are present. Ideally, dietary means should be used to attain even lower levels of LDL-cholesterol, if possible, to achieve a further reduction in CHD risk.

Although the goal of therapy is to lower the LDL-cholesterol concentration, measurement of serum total cholesterol can be used to monitor the response to diet. The principle is that LDL-cholesterol should be used for the definitive classification of patients and for decision making, but total cholesterol can be substituted for monitoring. For simplicity, a serum total cholesterol of 240 mg/dL corresponds roughly to an LDL-cholesterol of 160 mg/dL, while a total cholesterol of 200 mg/dL corresponds roughly to an LDL-cholesterol of 130 mg/dL. Thus, as a guide for monitoring, the minimal goals of therapy are: (1) to lower total cholesterol to below 240 mg/dL, if the patient has neither definite CHD nor two other CHD risk factors, or (2) to lower total cholesterol to below 200 mg/dL, if definite CHD or two other risk factors are present. It should be emphasized again that even lower levels of total cholesterol are desirable. The use of total cholesterol as a surrogate for LDL-cholesterol applies to patients with average levels of HDL-cholesterol without high total triglyceride levels. If the patient is found to have an abnormally high or low HDL-cholesterol or hypertriglyceridemia on initial classification, so that total cholesterol is not a good surrogate for LDL-cholesterol, it is appropriate to use LDL-cholesterol even in monitoring. After the cholesterol response to diet has been obtained, LDL-cholesterol should again be measured in order to decide whether or not the goal of therapy has been achieved. In addition, levels of LDL-cholesterol should be employed for making a decision about drug therapy.

Overview and General Approach

Three dietary habits typically contribute significantly to elevated plasma cholesterol. First is a high intake of saturated fatty acids. The average intake is 13% to 15% of total calories, but many Americans consume 15% to 20% of their calories as saturated fatty acids. Second is a relatively high intake of cholesterol. Many patients with high-risk LDL-cholesterol levels exceed the current average intake of about 350 to 450 mg/d. Third is a high caloric intake that exceeds body requirements commonly causing obesity. The aim of dietary therapy is to reverse these excesses while maintaining and promoting good nutrition.

This document is directed at the high-risk patient, and its underlying theme is specific therapy for high blood cholesterol. Modification of the diet is an essential element in this therapy. The initial diet modifications recommended for patients in this report are very similar to the diet modifications recommended by the American Heart Association (Dallas) and other organizations for the public at large, as part of a population-based approach for lowering cholesterol. In the program described in this report, however, diet recommendations are provided to patients, in a medical treatment setting, in an intensive manner. Accordingly, the dietary intervention described here is referred to as "dietary treatment." It should be noted that the diets recommended in this report are consistent with good nutrition, and that their aim is to achieve healthy eating patterns. Physicians should emphasize to patients that the goal is not a temporary "diet," but a permanent change in eating behavior.

Diet modification should occur in two steps, which are outlined and compared in Table 6. These diets are designed to progressively reduce the intake of saturated fatty acids and cholesterol and eliminate excess total calories. The Step-One Diet should be prescribed by the physician and implemented by the physician and his or her immediate staff. This diet calls for an intake of total fat less than 30% of calories, saturated fatty acids less than 10% of calories, and cholesterol less than 300 mg/d. The patient's serum cholesterol level should be measured at four to six weeks and at three months after starting the Step-One Diet.

If the minimal goals of therapy are not achieved on this diet by three months, the patient should usually progress to the Step-Two Diet. Adoption of the Step-Two Diet would be facilitated by referral to a registered dietitian. This diet

calls for a further reduction in saturated fatty acid intake to less than 7% of calories and cholesterol intake to less than 200 mg/d.

For many high-risk patients, the goals of cholesterol lowering can be achieved by dietary therapy alone. It is important that dietary therapy not be regarded as a failure prematurely. For most patients, dietary therapy should be continued for at least six months before adding drug therapy. Exceptions include patients with very-high LDL-cholesterol levels and other severe dyslipidemias (see Appendix II). If the desired goals of LDL-cholesterol lowering are met by diet modification alone, long-term monitoring is indicated. If reduction of LDL-cholesterol is not satisfactory, lipid-lowering drugs should be considered along with continued dietary intervention. (For detailed information about the effects of diet on serum lipids and lipoproteins and on CHD risk, including key studies and reviews, the reader should consult references 26 through 46.)

Recommended Diets

Step-One and Step-Two Diets—Nutrients and Rationale.—The recommended diets are presented in two steps—the Step-One and Step-Two Diets. The Step-One Diet calls for the reduction of the major and obvious sources of saturated fatty acids and cholesterol in the diet; for many patients this can be achieved without a radical alteration in dietary habits. The Step-Two Diet requires careful attention to the whole diet so as to reduce the intake of saturated fatty acids and cholesterol to a minimal level compatible with an acceptable and nutritious diet. Saturated fatty acids and cholesterol are not essential nutrients, and neither is required in the diet. The body can make these lipids in abundance, and they can be transported from one tissue to another to assure that any local shortage is supplied by lipids produced elsewhere in the body. The real need then is to reduce dietary saturated fatty acids and cholesterol to the levels required to achieve the goals of LDL-cholesterol lowering and still provide a diet that is nutritious and palatable. The fat-modified diets proposed in this report are designed to achieve these aims. The rationale for the recommended characteristics of the Step-One and Step-Two Diets can be described briefly.

A Nutritionally Balanced Diet.—A prerequisite for any therapeutic diet is that it be nutritionally adequate.[47] It must contain sufficient amounts of vitamins, minerals, and macronutrients to meet recommended allowances. The diet should contain a variety of foods. Fruits, vegetables, and legumes (peas and beans) are good sources of vitamin A, vitamin C, folic acid, fiber, and many minerals. Whole-grain and enriched breads, cereals, and other grain products contain B vitamins, protein, fiber, and some iron. Poultry and fish are good sources of protein. Meat products are rich in protein and contain iron in a form that is well absorbed; thus, meat can be included in a diet otherwise designed to lower serum cholesterol, although meat fat needs to be curtailed. The same is true of milk products; the nonfat portion of milk is rich in calcium and contains protein. While egg yolks are rich in cholesterol, egg whites contain protein and no cholesterol. Most nuts contain protein and fat, but their fat is largely unsaturated and thus does not raise the serum cholesterol level. Thus, while a serum-cholesterol-lowering diet requires modification of fat, the diet should be nutritious and palatable and include a variety of foods. The following considers the specific modifications that will be required.

Total Fat.—Total fat intake in both therapeutic diets should not exceed 30% of total calories. The purpose of decreasing total fat intake is twofold—to facilitate reduction of saturated fatty acid intake and to promote weight reduction in overweight patients by substituting foods of lower caloric density. Total fat in the current American diet averages approximately 35% to 40% of calories. Hence, for most high-risk patients, about one-fifth of their total fat now consumed must be eliminated. In the past, one approach to more intensive dietary therapy of high blood cholesterol (beyond the Step-One Diet) has been to reduce intake of total fat to 20% or less of calories, in parallel with progressive reductions in saturated fatty acids and cholesterol. However, very low fat intakes have low satiety value and often are not well accepted. Recent evidence indicates that a marked reduction in dietary fat is not required for satisfactory lowering of plasma LDL, provided that saturated fatty acids are reduced and the remaining fat is mainly unsaturated. In other words, a decrease in total fat to below 30% of calories may not be needed for the sole purpose of lowering the plasma cholesterol level. Nevertheless, a reduction in total fat to near 20% of calories will facilitate weight reduction and a decrease in saturated fatty acid intake for some patients. For these reasons, a further reduction of fat intake is not required in the Step-Two Diet, but neither is it excluded.

Saturated Fatty Acids.—In the Step-One Diet, saturated fatty acids should be decreased to less than 10% of calories. For most patients, saturated fatty acid intake will have to be reduced by about one-third to meet the requirements of the Step-One Diet, and another third for the Step-Two Diet. Several dietary fats are rich in saturated fatty acids. Animal fats that are high in saturated fatty acids include butter fat—contained in butter itself, whole milk, cream, ice cream, and cheese—beef fat, and pork fat. In addition, three plant oils—palm oil, palm kernel oil, and coconut oil—are especially rich in saturated fatty acids.

Polyunsaturated Fatty Acids.—When dietary saturated fatty acids are decreased, they can be replaced in part by polyunsaturated fatty acids. The polyunsaturates can be increased to 10% of calories, but they should not exceed this value. The current American diet contains about 7% of calories as polyunsaturated fatty acids, which should be a minimum value for the therapeutic diets. There are two major categories of polyunsaturated fatty acids, commonly referred to as omega-6 and omega-3. The major omega-6 fatty acid is linoleic acid, which has 18 carbon atoms and two double bonds. Substitution of linoleic acid for dietary saturated fatty acids results in a fall in the plasma cholesterol level. Although very high intakes of linoleic acid were once advocated for cholesterol lowering, lack of information about the consequences of long-term ingestion of large amounts of linoleic acid has led most investigators to recommend a ceiling of 10% of total calories. Several vegetable oils are rich in linoleic acid, including safflower oil, sunflower seed oil, soybean oil, and corn oil. Although polyunsaturated oils are high in linoleic acid and low in saturated fatty acids, they also are high in total calories (as are all fats and oils); consequently they can promote weight gain if consumed in large amounts.

The major sources of omega-3 fatty acids are the fish oils. Most omega-3 fatty acids in fish oil have very elongated carbon chains and are highly polyunsaturated. The major acids in this class are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The omega-3 fatty acids have been found to lower triglyceride levels when given in high doses, but they are not necessarily the desired therapy for hypertriglyceridemia (Appendix II). There is little evidence that omega-3 fatty acids are useful for reducing LDL-cholesterol levels. Although it has been postulated

by some that they will reduce the risk for CHD, this has not been established. Furthermore, it is not known whether long-term ingestion of these fatty acids will lead to undesirable side effects. The use of fish-oil capsules as a supplement in a therapeutic diet for high-risk cholesterol levels is not recommended here.

Consumption of omega-3 fatty acids should be differentiated from that of fish. Some fish are rich in omega-3 acids while others are not. Epidemiologic data suggest that frequent consumption of fish of any type, seemingly independent of omega-3 fatty acids, is associated with reduced CHD risk. Whether this is true or not, fish can serve as a useful substitute for meats that are richer in saturated fatty acids.

Monounsaturated Fatty Acids.—In both therapeutic diets, monounsaturated fatty acids, mainly oleic acid, should comprise 10% to 15% of total calories. Oleic acid is the major fatty acid found in olive oil, rapeseed (canola oil), and high-oleic forms of sunflower seed oil and safflower oil. For many years, oleic acid was considered to be "neutral" in its effect on plasma cholesterol, neither raising nor lowering the cholesterol level. However, recent evidence indicates that oleic acid may cause as much of a decrease in LDL-cholesterol levels as linoleic acid when either is substituted for saturated fatty acids in the diet. The current American diet contains 14% to 16% of calories as monounsaturated fatty acid. Much of it is consumed with animal fats, which are rich in saturated fatty acids. When animal fats are curtailed, a larger portion of monounsaturated fatty acids can come from vegetable oils.

Dietary Cholesterol.—Dietary cholesterol causes marked hypercholesterolemia and atherosclerosis in many laboratory animals, including nonhuman primates. Although high intakes of cholesterol in humans rarely cause striking rises in the plasma cholesterol level, controlled metabolic studies show that dietary cholesterol usually raises the plasma cholesterol level. The degree of rise varies from person to person. Overall, excess dietary cholesterol appears to contribute to the high LDL-cholesterol levels seen in high-risk patients and thus may add to CHD risk. Furthermore, concern about dietary cholesterol extends beyond its effects in raising the LDL-cholesterol level. Newly absorbed cholesterol enters the circulation with chylomicrons, which are degraded to cholesterol-rich chylomicron remnants; the latter may be atherogenic. Dietary cholesterol is not required for normal body function.

For practical purposes, a cholesterol intake of less than 300 mg/d is reasonable as part of the first step in dietary management of high-risk LDL-cholesterol. However, further restriction, as recommended in the Step-Two Diet, is justified for patients who do not achieve the goals of therapy on the Step-One Diet, despite adherence. Cholesterol in the diet comes from animal products. Particularly rich sources are egg yolk and organ meats (liver, sweetbreads, and brain). Some shellfish (eg, shrimp) also are moderately high in cholesterol, but not to the extent of egg yolk or organ meats. The flesh of all animals (beef, pork, lamb, chicken, fish) contains cholesterol; it is present in both muscle and fat, and both have approximately the same concentrations on a wet-weight basis. Dairy products containing butter fat also contribute cholesterol to the diet.

Protein.—The recommended intake of protein in both therapeutic diets is between 10% and 20% of calories. In laboratory animals, certain plant proteins have a cholesterol-lowering action relative to animal proteins. The same effect has not been established in humans. Thus, the type of protein in the therapeutic diets is not specified.

Carbohydrate.—Both recommended diets specify an intake of carbohydrates of 50% to 60% of calories. When dietary fat is reduced, it should be replaced by carbohydrate. Dietary carbohydrates include simple sugars (monosaccharides and disaccharides), complex digestible carbohydrates (starches), and complex indigestible carbohydrates (fiber). Complex carbohydrate should comprise more than half of digestible carbohydrates; this will help ensure ingestion of desirable quantities of vegetable products that contain vitamins, minerals, and fiber. In most people, when digestible carbohydrates are substituted for cholesterol-raising saturated fatty acids, the LDL-cholesterol level will fall to about the same extent as when oleic acid and linoleic acid are substituted in this manner. Very-high-carbohydrate diets can raise plasma triglycerides, but when fat intakes are in the vicinity of 30% of calories, this triglyceride response is minimal.

Total Calories.—Obesity is not only associated with elevated serum LDL-cholesterol levels, but is an independent risk factor for CHD. An important recommendation, therefore, is to reduce caloric intake to achieve weight reduction in overweight patients. Weight reduction will lower the LDL-cholesterol level in many people, as well as reduce plasma triglycerides and raise HDL-cholesterol levels. Some patients with high-risk LDL-cholesterol levels are extremely sensitive to caloric intake, and weight reduction and establishment of desirable body weight will completely correct their elevated LDL-cholesterol concentrations. The importance of caloric restriction in overweight, high-risk individuals cannot be overemphasized.

Weight reduction can be facilitated by exercise. Experience has shown that regular exercise will curb the appetite as well as burn off excess calories. It also will lower serum triglycerides and raise HDL-cholesterol levels, and, in some individuals, may lower the LDL-cholesterol level.

Fiber.—The indigestible carbohydrates and related polymers come under the category of dietary fiber. One type of fiber is insoluble, an example of which is the cellulose found in wheat bran. Insoluble fiber adds bulk to the stools and contributes to normal colon function. Some authorities believe that a relatively high intake of dietary fiber may help prevent diverticulosis and colon cancer, although this remains to be proven. Excessive intakes of insoluble fibers can be associated with gastrointestinal side effects and even interfere with absorption of vital nutrients such as calcium. Dietary fibers such as cellulose appear to have very little or no effect on blood cholesterol levels.

Another type of fiber is soluble in the intestine but not absorbed. This category includes pectins, certain gums, and psyllium. One of the gums is β-glucan, which is present in oat products and beans. High intake (eg, 15 to 25 g/d) of soluble fiber has been reported to lower the plasma cholesterol level by 5% to 15%. This high intake can produce gastrointestinal side effects, but prolonged usage frequently is associated with improved tolerance.

Alcohol.—The average intake of alcohol among Americans is approximately 5% of total calories, but this value varies widely among individuals. Although alcohol is not harmful when taken in moderation, a high consumption is known to have many adverse effects on health. Alcohol affects lipoprotein metabolism in several ways. It does not affect LDL-cholesterol concentrations, but it does increase triglyceride concentrations and HDL-cholesterol levels in many individuals. The mechanism for the rise in HDL-cholesterol is not known, nor is it known whether the higher level so produced imparts any protection against CHD. For patients who can consume moderate amounts of alcohol responsibly, its use can be allowed in the context of

Table 7.—Recommended Diet Modifications to Lower Blood Cholesterol

	The Step-One Diet	
	Choose	Decrease
Fish, chicken, turkey, and lean meats	Fish, poultry without skin, lean cuts of beef, lamb, pork or veal, shellfish	Fatty cuts of beef, lamb, pork; spare ribs, organ meats, regular cold cuts, sausage, hot dogs, bacon, sardines, roe
Skim and low-fat milk, cheese, yogurt, and dairy substitutes	Skim or 1% fat milk (liquid, powdered, evaporated), buttermilk	Whole milk (4% fat): regular, evaporated, condensed; cream, half and half, 2% milk, imitation milk products, most nondairy creamers, whipped toppings
	Nonfat (0% fat) or low-fat yogurt	Whole-milk yogurt
	Low-fat cottage cheese (1% or 2% fat)	Whole-milk cottage cheese (4% fat)
	Low-fat cheeses, farmer or pot cheeses (all of these should be labeled no more than 2 to 6 g of fat per ounce)	All natural cheeses (eg, blue, roquefort, camembert, cheddar, Swiss), low-fat or "light" cream cheese, low-fat or "light" sour cream, cream cheeses, sour cream
	Sherbet, sorbet	Ice cream
Eggs	Egg whites (2 whites equal 1 whole egg in recipes), cholesterol-free egg substitutes	Egg yolks
Fruits and vegetables	Fresh, frozen, canned, or dried fruits and vegetables	Vegetables prepared in butter, cream, or other sauces
Breads and cereals	Homemade baked goods using unsaturated oils sparingly, angel food cake, low-fat crackers, low-fat cookies	Commercial baked goods: pies, cakes, doughnuts, croissants, pastries, muffins, biscuits, high-fat crackers, high-fat cookies
	Rice, pasta	Egg noodles
	Whole-grain breads and cereals (oatmeal, whole wheat, rye, bran, multigrain, etc)	Breads in which eggs are a major ingredient
Fats and oils	Baking cocoa	Chocolate
	Unsaturated vegetable oils: corn, olive, rapeseed (canola oil), safflower, sesame, soybean, sunflower	Butter, coconut oil, palm oil, palm kernel oil, lard, bacon fat
	Margarine or shortenings made from one of the unsaturated oils listed above, diet margarine	
	Mayonnaise, salad dressings made with unsaturated oils listed above, low-fat dressings	Dressings made with egg yolk
	Seeds and nuts	Coconut

the above reservation. However, this report does not specifically recommend use of alcohol in the prevention of CHD.

Expected Responses to Dietary Therapy.—The degree of reduction of LDL-cholesterol levels that can be achieved by dietary therapy depends on the dietary habits of the patient before starting the diet and on the inherent responsiveness of the patient. In general, patients with high cholesterol levels show a greater absolute reduction in total and LDL-cholesterol concentrations than do individuals with relatively low cholesterol levels. Metabolic ward studies suggest that switching from the typical American diet to the Step-One Diet could reduce cholesterol levels on average by 30 to 40 mg/dL. Advancing to the Step-Two Diet can be expected to cause a further decline of approximately 15 mg/dL in cholesterol levels. Some individuals may demonstrate even greater reductions on the two diets, and others will have lesser responses. Most of the decrease in total blood cholesterol occurs in the LDL fraction.

Practical Approach to Dietary Therapy

Outline of Approach.—Once a patient is deemed at high risk, dietary therapy should begin in the physician's office. Diet is the cornerstone of treatment of high-risk cholesterol levels. The view that diet modification is impractical or doomed to failure for most patients is not justified. Many individuals have successfully modified their diets and have obtained a substantial reduction in cholesterol levels. Much of the problem of high cholesterol levels among Americans is due to dietary excesses, and diet modification is the rational approach to this problem for most people.

Role of the Physician.—The success of dietary therapy will depend to a large extent on the physician's attitudes, knowledge, and skills in motivating the patient and in organizing a team approach to dietary therapy. The physician can have a major impact on the patient's attitude toward diet modification. A positive attitude on the part of the physician is absolutely vital. The physician should describe to the patient his/her category of high blood cholesterol and should give an overview of the therapeutic plan. The role of diet, and possibly drugs, should be discussed. The physician will need to review the patient's dietary history. The patient should be questioned about current dietary habits with special attention to intake of foods rich in saturated fatty acids and cholesterol (eg, dairy fats—milk, butter, cheese, ice cream—frequency and choices of meat products, bakery goods, eggs, and organ meats). The need to modify eating behavior to achieve the

goals of therapy should be indicated, and the plan for carrying out dietary treatment, as it involves other members of the team, can be described. Finally, the physician has a vital role to play in the monitoring of response, in reinforcement of the diet message, and in leadership of the therapeutic team. For assessing adherence to the diet, the physician can review the contents of Table 7 with the patient at follow-up visits.

Role of the Physician's Staff.—Another key component of the therapeutic team is the physician's staff. This may include registered nurses, registered physician's assistants, nurse clinicians, and other types of assistants. These individuals should receive appropriate training for their roles in patient management, which will include aiding in further dietary assessment and in dietary education and counseling. Nurses and other assistants can play key roles in patient education (eg, rationale for dietary change, selection of appropriate foods), in promoting behavioral changes, and in monitoring dietary changes. Various educational materials produced by the National Cholesterol Education Program and the American Heart Association can be used to assist in dietary education for patients. Referral to a registered dietitian can facilitate dietary instruction and monitoring of adherence, but if the physician's staff is appropriately trained, it can perform these functions for many patients.

Role of Registered Dietitians.—Registered dietitians (RDs) are educated in the science of nutrition and are professionally trained in dietary intervention. They must meet uniform standards for registration. The term "nutritionist" is used in a variety of ways. Some nutritionists are registered dietitians, but others may not be registered and may not have the clinical training in dietary counseling of a registered dietitian. Although such nutritionists may play a role in dietary education, referral to a registered dietitian is particularly valuable for more intensive dietary therapy, such as the Step-Two Diet, and evaluation of nutritional adequacy. Patients who have had difficulty in adhering or responding to the Step-One Diet also have much to gain from counseling by a registered dietitian. Patients who are not initially successful in the Step-One Diet may be referred to a dietitian for another Step-One Diet trial period before progressing to the Step-Two Diet. For some patients, based on the physician's judgment, referral to a registered dietitian may be appropriate from the outset of dietary therapy.

Dietitians can be identified through a local hospital as well as through state and district affiliates of the American Dietetic Association (208 S LaSalle St, Chicago, IL 60604). The American Dietetic Association maintains a roster of dietitians and responds to requests in writing for assistance in locating a registered dietitian in a given area. Dietitians with particular expertise in cholesterol management are available in most large medical centers where they are often part of a multidisciplinary lipid clinic team or cardiac rehabilitation team. The local affiliate of the American Heart Association may have a listing of dietitians who have particular interest and expertise in modifying the diet for purposes of cardiovascular risk reduction.

Schedule of Dietary Therapy.—Adherence to the prescribed diet is facilitated by monitoring the patient's response. The Step-One Diet should be employed for three months, and if the desired response is not obtained in spite of good diet adherence, the patient can progress to the Step-Two Diet for another three months. During this period, serum cholesterol levels should be monitored at regular intervals (described below). For most patients, dietary therapy to lower serum total and LDL-cholesterol should be employed for at least six months before considering drugs. Exceptions to this approach are patients with severe elevations of serum cholesterol (Appendix II) and patients with definite CHD.

Recommended Dietary Patterns.—Most patients should be able to adopt and adhere to the Step-One Diet. Table 7 outlines ways to achieve the goals of dietary therapy, and a copy may be given to the patient along with additional educational materials. It should be emphasized to the patient that the recommended diet can be both tasty and nutritious, and that many choices of high-quality and acceptable foods are available in stores and restaurants.

A few general dietary changes underlie implementation of the Step-One Diet. To decrease intake of total fat, saturated fatty acids, and cholesterol, attention should be given to reducing foods containing butter fat—butter itself, cheese, ice cream, cream, whole (4%) milk, and even 2% milk. Only lean cuts of meat should be selected, visible fat should be trimmed away, and fat should be allowed to drain from meat after cooking. The skin of chicken should be removed, and fish should be substituted frequently for meat. Consumption of egg yolks and organ meats (liver, brain, sweetbreads) should be reduced. Shrimp, lobster, and other shellfish contain varying amounts of cholesterol, but are low in fat, and thus may be eaten occasionally. The vegetable oils rich in saturated fatty acids—coconut oil, palm kernel oil, and palm oil—are used in some commercial foods and food products; products that list these oils as ingredients on the label should generally be avoided.

Specific Food Subgroups.—Special attention should be given to certain common foods in the diet. This subsection provides specific recommendations:

MEATS.—Beef, pork, and lamb.—Use *lean* cuts of beef, pork, and lamb. Lean cuts of beef include extra-lean ground beef, sirloin tip, round steak, rump roast, arm roast or center-cut ham, loin chops, and tenderloin. Trim all fat off the outside of meats before cooking. It is not necessary to severely curtail the intake of red meat. Lean meat is rich in protein and contains a highly absorbable form of iron. Premenopausal women in particular should avoid severe reduction of lean red meat that would increase the risk for iron-deficiency anemia.

Processed meats.—Eat very little high-fat processed meats—bacon, bologna, salami, sausage, and hot dogs. Processed meats contain large quantities of "hidden" fat, and they are not rich in valuable nutrients.

Organ meats.—The organ meats—liver, sweetbreads, kidneys, and brain—are very rich in cholesterol, and they should be limited.

Chicken and turkey.—These are good sources of protein. The fat of poultry should be reduced by removal of skin and underlying fat layers. Chicken and turkey can be substituted for lean red meat in the diet, but they do not contain as much iron. Chicken and poultry should not be fried in fats rich in saturated fatty acids or covered with fat-rich sauces.

Fish.—Fish are a good source of protein. They contain cholesterol, but usually are low in saturated fatty acids. The preparation of fish is important. Like chicken and turkey, they should not be fried in saturated fats or covered with fat-rich sauces.

Shellfish.—Most shellfish contain less fat than meat and poultry. Their cholesterol content is variable (see Table 8). Some shellfish (eg, shrimp) are relatively high in cholesterol, but even these can be eaten occasionally within the recommended guidelines for cholesterol intake.

A reasonable approach to meat consumption is to limit intake of lean meat, chicken, turkey, and fish to six ounces

Table 8.—Cholesterol and Fat Content of Animal Products in Three-Ounce Portions (Cooked)

Source	Cholesterol Content, mg/3 oz	Total Fat Content, g/3 oz
Red meats (lean)		
Beef	77	8.7
Lamb	78	8.8
Pork	79	11.1
Veal	128	4.7
Organ meats		
Liver	270	4.0
Pancreas (sweetbreads)	400	2.8
Kidney	329	2.9
Brains	1746	10.7
Heart	164	4.8
Poultry		
Chicken (without skin)		
Light	72	3.8
Dark	79	8.2
Turkey (without skin)		
Light	59	1.3
Dark	72	6.1
Fish		
Salmon	74	9.3
Tuna, light canned in water	55	0.7
Shellfish		
Abalone	90	0.8
Clams	57	1.7
Crab meat		
Alaskan King	45	1.3
Blue crab	85	1.5
Lobster	61	0.5
Oysters	93	4.2
Scallops	35	0.8
Shrimp	166	0.9

per day. The cholesterol and total fat content per three ounces (the recommended portion size) of various cooked meats are presented in Table 8.

Dairy Products.—Use skim milk or 1% milk instead of 2% or whole milk, which contains approximately 4% fat. Decrease natural and processed cheeses; substitute low-fat (2%) cottage cheese or synthetic cheeses produced from vegetable oils. Choose yogurt of the nonfat or low-fat (1% to 2%) type. Experiment with evaporated skim milk in recipes calling for heavy cream. Substitute low-fat yogurt or low-fat cottage cheese for sour cream in dips and salad dressings. Have at least two servings of very-low-fat dairy products, such as two glasses of skim (or 1%) milk, daily to help maintain calcium intake.

Fats and Oils.—The general rule is to reduce intakes of fats and oils that are high in saturated fatty acids and cholesterol. Butter fat is high in both and should be curtailed as much as possible. Lard and beef fat are other blood cholesterol–raising animal fats. Vegetable fats do not contain cholesterol. However, certain vegetable fats—coconut oil, palm oil, and palm kernel oil—are very high in saturates and should be avoided; these fats are often used in bakery goods, processed foods, popcorn oils, and nondairy creamers. Labels on these foods should be read carefully to detect the presence of saturated vegetable oils.

Unsaturated vegetable oils and fats do not raise blood cholesterol but they should be limited because they are high in calories. Generally, up to six to eight teaspoons a day is acceptable. Desirable liquid vegetable oils are corn oil, cottonseed oil, olive oil, rapeseed (canola) oil, safflower oil, soybean oil, and sunflower oil. Peanut oil is less desirable, but small amounts are acceptable. Margarine represents partially hydrogenated vegetable oil and is preferable to butter. Vegetable shortenings fall into the same category as margarine. Both contain quantities of *trans* fatty acids; these are not naturally occurring and should not be taken in excess. Mayonnaise and salad dressings often are made from unsaturated fats, but they too should be limited because of their high caloric content.

Eggs.—Eat no more than three egg yolks in a week on the Step-One Diet, and no more than one per week on the Step-Two Diet. Egg yolks often are hidden in cooked and processed foods. Egg whites contain no cholesterol, and they can be eaten often. Experiment with one to two egg whites instead of whole eggs in recipes, or use commercial egg substitutes that do not contain yolk.

Fruits and Vegetables.—It is advisable to feature fruits and vegetables as an important part of each meal. Both are rich in vitamins, fiber, and some minerals, and contribute to achieving the recommended allowances of these nutrients. Certain green and yellow vegetables may reduce the risk for cancer. Fruits (and even vegetables) can be used for snacks and desserts.

Breads, Cereals, Pasta, Rice, Dried Peas, and Beans.—These products are high in carbohydrate and protein and most are low in fat. Therefore, they can be increased in the diet as substitutes for fatty foods. However, they too contain calories and must not be eaten in excess. Cereals can be eaten as snacks as well as for breakfast. Dried peas and beans are good sources of protein. Combine large quantities of pasta, rice, legumes, and vegetables with smaller amounts of lean meat, fish or poultry to derive complete protein sources with less fat and calories.

Nuts.—Nuts tend to be high in fat, but the fat usually is unsaturated. The intake of nuts should thus be limited mainly to avoid excess calories. The same is largely true for peanut butter.

Other Eating Tips.—Snacks.—Most candies should be limited as snacks; they tend to be rich in simple sugars and fats, and their caloric content outweighs their nutritional value. Some good choices in snacks are graham crackers, rye krisp, melba toast, soda crackers, bagels, English muffins, fruit, ready-to-eat cereals, and vegetables; these are preferable to snack crackers, french fries, and chips. Popcorn should be air popped or cooked in small amounts of liquid vegetable oil.

Desserts.—Eat fruits, low-fat fruit yogurt, and fruit ices instead of pastries, cake, and cookies. Also acceptable are sherbet, angel food cake, jello, frozen low-fat yogurt, and, occasionally, ice milk.

Cooking Methods.—Choose those methods that use little or no fat. They include steaming, baking, broiling, grilling, or stir-frying in small amounts of fat. Foods can be cooked in the microwave or in a nonstick pan without added fat. Limit fried foods and avoid frying in saturated fat. Soups and stews should be chilled after cooking, and the congealed fat that forms on top after a few hours in the refrigerator should be skimmed off. When preparing meals avoid use of excess sodium, which can contribute to raising blood pressure in some people.

Eating Away From Home.—Order entrees, potatoes, and vegetables without sauces or butter. When meat exceeds the size of a deck of cards (three to four ounces), the rest can be taken home for another meal. Choose

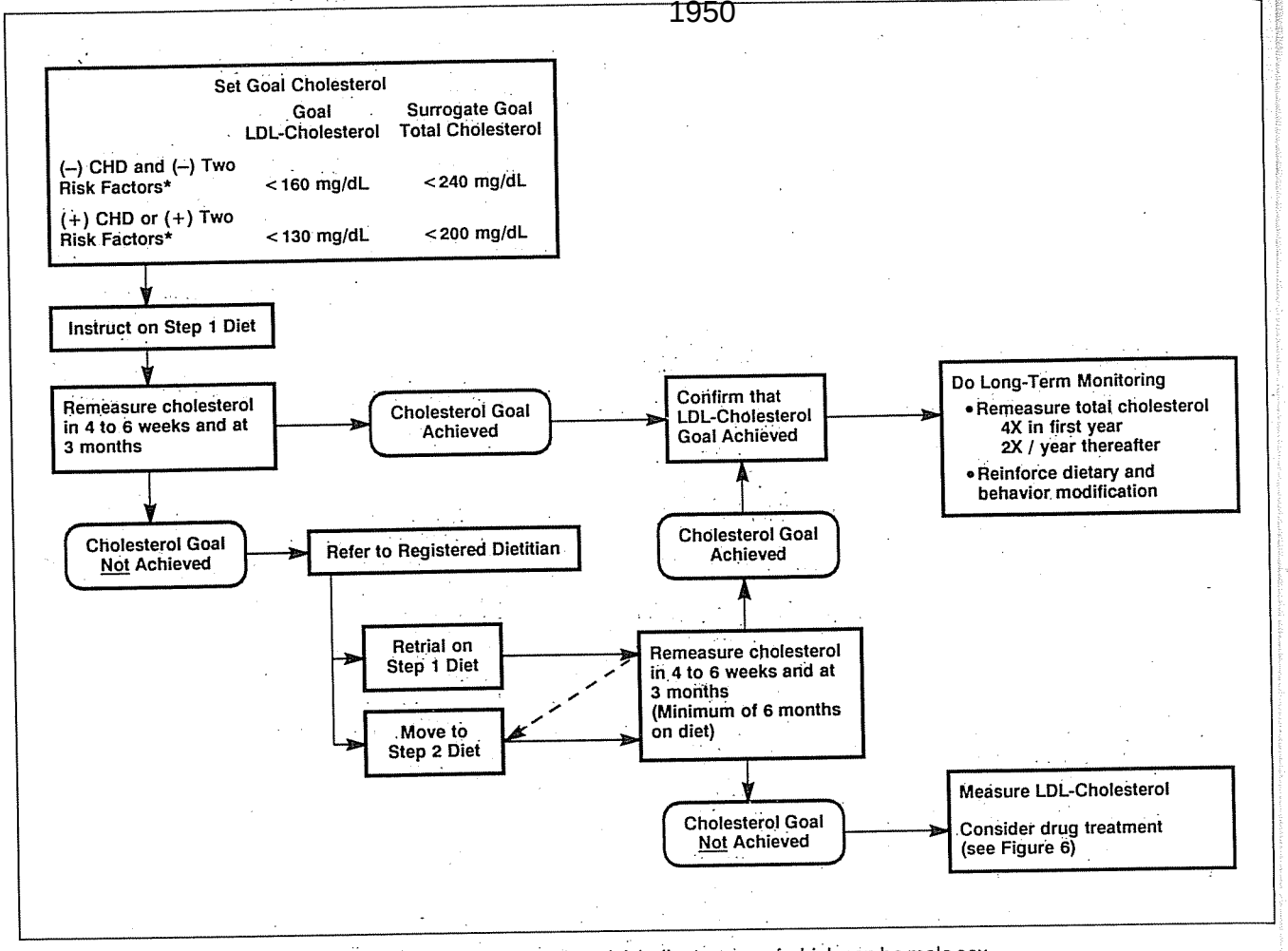

Fig 5.—Dietary treatment. Asterisk indicates one of which can be male sex (Table 4); LDL, low density lipoprotein; CHD, coronary heart disease.

vegetable or fruit salads, and ask for salad dressings to be served on the side; use dressings sparingly. Limit high-fat toppings such as bacon, crumbled eggs, cheese, sunflower seeds, and olives, the latter two because they may be high in fat and salt. Ask for margarine instead of butter, and limit the amount of margarine used on bread and baked potatoes.

The physician who follows patients with high blood cholesterol frequently will be asked about specific food items. It may be helpful for the physician to have available a reference on food composition.[48,49]

Behavioral Modification.—Long-term adherence to the recommended diets can be achieved only through permanent modification of eating behavior. Several factors are required to achieve long-term success in adapting to a new diet. The rationale for diet change can be provided by the physician. Education of the patient in the principles of the fat-modified diet is the responsibility of the physician, the physician's immediate staff (eg, nurses), and, when utilized, a registered dietitian. The effectiveness of this approach will be facilitated by frequent communication among the different members of the team. Followup and monitoring by physicians is a key element in achieving the goals of LDL lowering on a long-term basis. Sometimes, permanent modification of eating behavior will require prolonged interaction with a registered dietitian. A brief summary of the process of dietary instruction and behavior modification as practiced by dietitians is provided in Appendix III. This discussion may guide physicians in their own instructions to the patient.

An important adjunct to long-term change in eating behavior and life-style is a regular exercise program. Especially useful forms of exercise are activities that require movement of the body over distance, such as walking, stair climbing, running, cycling, and swimming. Improvements in cardiovascular fitness result from exercising regularly at moderate intensity for 15 to 30 minutes at least every other day. However, vigorous exercise must be carried out with caution in high-risk persons, and only with the advice of a physician and under the supervision of trained personnel.

Monitoring and Followup

Step-One Diet.—After starting the Step-One Diet, the serum total cholesterol level should be measured at four to six weeks and at three months (Fig 5). This will allow the patient enough time to adopt new eating habits and to respond to the dietary change. At the end of three months, the physician should assess the patient's adherence to the diet plan and response to dietary therapy. The response can be judged on the basis of the change in serum cholesterol level. If the response is satisfactory, ie, if the total cholesterol monitoring goal is met (<240 mg/dL without definite CHD or two other risk factors, <200 mg/dL with definite CHD or two other risk factors [Table 4]), then the LDL-cholesterol level should be mea-

sured in order to confirm that the LDL-cholesterol goal has been met. If the LDL goal is met, the phase of long-term monitoring can begin. If the response is not satisfactory, the patient should generally be referred to a registered dietitian and should progress to the Step-Two Diet or to another trial on the Step-One Diet. If this latter approach is selected, the patient should again be evaluated after four to six weeks and three months, with progression to the Step-Two Diet if the response is still not satisfactory.

Step-Two Diet.—On the Step-Two Diet, serum cholesterol levels should be measured after three to four weeks and three months of therapy. After three months of treatment with the Step-Two Diet, the physician should again assess the patient's adherence and response to the diet. It is important to document the extent of adherence to the therapeutic diet. If the desired goal for serum cholesterol–lowering has been attained, and a measurement of LDL-cholesterol level confirms that the LDL goal has been met, long-term monitoring can begin; if not, consideration should be given to drug therapy.

Diet Success: Long-term Monitoring.—The patient who has achieved the target goals for lowering of LDL-cholesterol by dietary therapy can be declared a diet success. Monitoring of total cholesterol should be carried out on a long-term basis. The fat-modified diet should be maintained indefinitely and the patient should be encouraged to adhere to the recommended eating pattern. Diet education should be continued and reinforced, by a registered dietitian if necessary. The patient should be counseled quarterly for the first year of long-term monitoring and twice yearly thereafter.

Total serum cholesterol should be measured prior to each visit, and the results should be used at the counseling session. For patients who have no lipoprotein abnormalities other than elevated LDL-cholesterol, monitoring at six-month intervals is appropriate. In such patients, the total cholesterol measurement, which can be made with a nonfasting blood sample and is less expensive than lipoprotein analysis, will provide a reasonable index of the LDL-cholesterol level. Many patients who previously have had high cholesterol levels on the typical American diet are "diet sensitive," which explains their originally high level. This means that continuous attention must be given to dietary adherence to avoid a "relapse" to high cholesterol concentrations. If the patient redevelops an elevated cholesterol level, the procedure outlined above for dietary therapy of elevated LDL-cholesterol may have to be reinstituted.

Inadequate Response to Diet.—A patient who fails to achieve the goals for lowering of total cholesterol (or LDL-cholesterol) by dietary therapy should be classified as having an inadequate response to diet. This does not necessarily mean diet failure, because a significant reduction in cholesterol levels may have occurred by diet modification. There are four categories of inadequate response to diet that can be distinguished.

1. Patients who have severe elevations of serum cholesterol often cannot achieve the goals of serum cholesterol lowering by diet, no matter how strict the diet. For these patients (Appendix II), it is not necessary to wait for six months of dietary therapy before adding drugs to the regimen.

2. Some patients with high LDL-cholesterol levels are biologically relatively resistant to LDL lowering by diet modification and will not achieve the cholesterol lowering goal despite good adherence to diet.

3. Others will adhere poorly to diet in spite of an intensive effort by the physician and counselors. After a few months it will be obvious that these patients will not adhere to dietary recommendations. Some physicians have the mistaken belief that most patients fall into this category, but this certainly is not true. A concerted effort by the physician, immediate staff, and registered dietitian should minimize the size of this group of patients.

4. For still other patients, a more prolonged period of dietary therapy may be justified. Up to a year, or even longer, may be required for a patient to learn to modify the diet by changing both the pattern of diet and eating habits. There may be a tendency for some physicians to employ drugs too soon instead of making the effort to change the patient's dietary habits. This tendency must be resisted. Adequate time should be allowed for the patient to attempt to modify the diet to achieve the desired goals of therapy.

Dietary Therapy for Special Groups

Severe Primary and Secondary Lipid Disorders.—Patients with severe primary hypercholesterolemia (eg, familial hypercholesterolemia) deserve maximal dietary therapy, ie, the Step-Two Diet. However, many of these patients will not respond adequately to diet and will require drug therapy (see Appendix II). Patients with severe primary hypertriglyceridemia should receive special attention to dietary management, which is described in more detail in Appendix II. The role of the diet in the treatment of low HDL-cholesterol and diabetic dyslipidemia likewise is discussed in Appendix II.

Elderly High-Risk Patients.—When considering dietary therapy for elderly patients classified as high risk, the value of diet modification for prevention of atherosclerotic disease must be balanced against the possibility of inadequate or inappropriate nutrition, which is often a problem in the elderly. The Step-One Diet seems prudent in elderly patients classified as high risk, but overly restrictive diets probably should be avoided. Intensive dietary therapy (eg, the Step-Two Diet) is not advisable in most elderly patients. Sound clinical judgment is required in making a decision about diet modification in older individuals classified as high risk, particularly because adequate intakes of calories and protein can be a major problem among the elderly.

Pregnant Women.—Elevations in cholesterol and triglyceride levels occur during pregnancy, with maximum levels in the third trimester. These increased levels are not generally clinically significant, but rare cases of hypertriglyceridemia and pancreatitis have been reported. Thus, some investigators recommend that serum triglyceride levels be measured at about the 28th week of gestation. Triglyceride levels generally return to baseline within six weeks postpartum, but elevations in LDL-cholesterol may occasionally persist for six to nine months. Such a response may represent a predisposition to elevated cholesterol. The approach to hyperlipidemic women who become pregnant is discussed in Appendix II.

Approach to Borderline–High Blood Cholesterol Group

Assessment of Risk.—Individuals with cholesterol levels in the range of 200 to 239 mg/dL are classified as having borderline–high blood cholesterol. Several studies indicate that cholesterol concentrations in the borderline-high range impart an increased CHD risk as compared with lower levels. However, while there is a progressive increase in risk as the blood cholesterol level rises from 200 to 240 mg/dL, the absolute risk does not rise sharply if no other risk factors are present (Table 3, "Background section"). For this reason, it is not necessary to enter most

people with borderline–high blood cholesterol into active medical therapy. They nonetheless deserve to receive dietary information and cholesterol education as discussed below.

Special attention should be given to young adults with borderline–high blood cholesterol because they may be "tracking" toward the high-risk category later in life. In fact, many experts believe that young adults (20 to 39 years of age) with borderline–high blood cholesterol levels warrant full evaluation of serum lipoprotein fractions. This is an area where individualized clinical judgment is appropriate.

As with all patients, those with borderline–high blood cholesterol levels should be evaluated for other CHD risk factors and should be given preventive medical care for these factors if present. As indicated previously, patients in the borderline–high blood cholesterol group who have definite CHD or two other CHD risk factors (one of which can be male sex) should be managed in the same way as patients with high blood cholesterol levels.

Some experts believe that patients in the borderline–high blood cholesterol group who have one other major risk factor (eg, hypertension) also warrant lipoprotein measurements and possible dietary therapy. This is particularly so for young adults. Although this is not recommended here as a general approach for most patients with borderline–high blood cholesterol, it is clear that individualized clinical judgment and patient management is appropriate for this group.

Dietary Information and Patient Education.—For individuals with borderline–high blood cholesterol, intensive dietary therapy is not required. The population-based approach for lowering cholesterol levels in the entire community is expected, however, to have a significant impact on the diet and behavior of this group. Since these people are at increased risk for CHD, compared with individuals whose cholesterol levels are below 200 mg/dL, they should be made aware of the significance of their moderately increased risk and given information about how to modify the diet to lower the cholesterol level. The basic recommendation is for the patient to adopt an eating pattern similar to that of the Step-One Diet.

The same materials provided with the Step-One Diet might be made available to these patients by the physician and immediate staff, but intensive monitoring is not required. It should not be necessary to refer the patient to a registered dietitian, and the time devoted to patient instruction will be less than for the high-risk group. It is the physician's responsibility to inform the patient of his or her moderately increased risk, to advise changes in life-style and eating habits, to provide educational materials about diet, and to direct the individual to other sources of educational material. For instance, the local chapter of the American Heart Association usually stocks valuable materials containing dietary advice and practical approaches to diet modification. Sections of this report also can be copied for the patient.

Special attention should be given to dietary counseling of young adults with borderline–high blood cholesterol levels. They should be started on the Step-One Diet, but, in addition, they should be monitored for adherence and response more carefully than middle-aged patients in the same category. Young adults should be counseled on what to eat when away from home, and they should develop exercise habits that will be particularly useful as lifetime habits. Young adults who have an exceptionally high caloric intake because of a high level of exercise should be cautioned against excessive intake of saturated fatty acids, cholesterol, and protein.

Reevaluation.—At the least, a follow-up measurement of the patient's cholesterol level should be made at one year and then at one- to two-year intervals. More frequent followup or measurements of lipoprotein fractions can be made at the discretion of the physician. Extra attention should be given to the followup of young adults with borderline–high blood cholesterol. Periodic determinations of serum cholesterol will indicate the physician's heightened and continuing concern; knowledge that the cholesterol level will be checked periodically should motivate the patient to adhere to the recommended diet; and these measurements will enable the physician to detect an increase in cholesterol level to the high blood cholesterol range, should it occur.

DRUG TREATMENT

When to Consider Drug Therapy/Treatment Goals

LDL-Cholesterol Levels for Initiation of Drug Therapy.—Patients whose LDL-cholesterol levels remain high despite adequate dietary therapy should be considered for drug treatment. At least six months of intensive dietary therapy and counseling should usually be carried out before initiating drug therapy. In individuals with severe elevations of LDL-cholesterol (>225 mg/dL) or with definite CHD, in whom dietary therapy alone is unlikely to be adequate or in whom the urgency of achieving substantial cholesterol lowering is greater, it may be appropriate to try dietary therapy alone for a period shorter than six months before considering drug therapy. A minimum of three months of dietary therapy is required to establish an adequate baseline for evaluating the efficacy of subsequent drug therapy. A registered dietitian, working with the physician to design an adequate treatment plan and assess dietary adherence, may enhance the effectiveness of dietary therapy sufficiently to obviate the need for drugs.

The LDL-cholesterol levels at which drug therapy should be considered after an adequate trial of dietary therapy alone are as follows:

(1) ≥190 mg/dL (very-high-risk LDL-cholesterol) in patients without definite CHD or two other CHD risk factors, one of which can be male sex (Table 4).

(2) ≥160 mg/dL (high-risk LDL-cholesterol) in patients with definite CHD or two other CHD risk factors (Table 4).

Clinical judgment is required when using these guidelines to make decisions about initiating drug therapy. All individuals with LDL-cholesterol levels ≥190 mg/dL are candidates for drug therapy, but the need is less pressing in older women. Men with LDL-cholesterol values between 160 and 190 mg/dL who have any other major risk factor generally should receive drug therapy. In women, however, a more conservative approach to drug therapy is appropriate, in view of the fact that the absolute risk of CHD is lower in women than in men. Thus, for women with LDL-cholesterol levels between 160 and 190 mg/dL, two other major risk factors or definite CHD should be present before initiating drug therapy. The distribution of LDL-cholesterol levels in the population is listed in Appendix I. It should be emphasized that maximum dietary therapy would significantly alter this distribution and decrease the percent of both men and women being considered for drug therapy.

Maximal efforts should be made in all patients to lower cholesterol levels and CHD risk by nonpharmacological approaches, such as diet, weight control, exercise, and other life-style modifications (eg, quitting smoking). This is especially important in patients who have not reached

Table 9.—Summary of the Major Drugs for Consideration*

Drugs	Reduce CHD Risk	Long-term Safety	Maintaining Adherence	LDL-Cholesterol Lowering, %	Special Precautions
Cholestyramine, colestipol	Yes	Yes	Requires considerable education	15-30	Can alter absorption of other drugs, can increase triglyceride levels and should not be used in patients with hypertriglyceridemia
Nicotinic acid	Yes	Yes	Requires considerable education	15-30	Test for hyperuricemia, hyperglycemia, and liver function abnormalities
Lovastatin†	Not proven	Not established	Relatively easy	25-45	Monitor for liver function abnormalities, and possible lens opacities
Gemfibrozil‡	Not proven	Preliminary evidence	Relatively easy	5-15	May increase LDL-cholesterol in hypertriglyceridemic patients; should not be used in patients with gallbladder disease
Probucol	Not proven	Not established	Relatively easy	10-15	Lowers HDL-cholesterol; significance of this has not been established; prolongs QT interval

*CHD indicates coronary heart disease; LDL, low density lipoprotein; and HDL, high density lipoprotein.
†Recently approved by the Food and Drug Administration for marketing.
‡Not approved by the Food and Drug Administration for routine use in lowering cholesterol. The results of the Helsinki Heart Study should be available soon to define the effect on CHD risk and long-term safety.

their minimal LDL-cholesterol goal on dietary therapy alone, but who do not qualify for drug treatment according to the above guidelines. These patients include those without definite CHD or two other risk factors (see Table 4), whose LDL-cholesterol levels are in the range of 160 to 190 mg/dL, and those with definite CHD or two other risk factors, whose LDL-cholesterol levels are 130 to 160 mg/dL, on adequate dietary therapy. While drug therapy is not routinely recommended for such patients, consideration should be given to the use of low doses of bile acid sequestrants, especially in men. The sequestrants have a proven record of long-term safety. Moreover, many experts feel that patients with definite CHD should receive drug therapy if their minimal LDL-cholesterol goal (<130 mg/dL) has not been reached.

Low density lipoprotein–cholesterol is the best parameter to use in making the decision to use drugs and for monitoring the response to drug therapy (at least in the first few months). The decision to initiate drug treatment usually commits the patients to long-term therapy, for years or even for life. Since the number of potential patients who are candidates for prolonged administration of drugs is substantial, all decisions to initiate drug therapy must be made only after careful deliberation. Dietary therapy is clearly the safest treatment available. Hence, maximal efforts at dietary therapy should be made before initiating drug therapy, and should be continued even if drug therapy is needed. (For detailed information about the effects of drugs on serum lipids and lipoproteins and on CHD risk, including key studies and reviews, the reader should consult references 7, 10-13, and 50-60.)

Target Treatment Levels of LDL-Cholesterol.—The minimum goals of drug therapy are the same as those of dietary therapy, and are as follows:

(1) LDL-cholesterol <160 mg/dL in patients without definite CHD or two other CHD risk factors (one of which can be male sex, [Table 4]).

(2) LDL-cholesterol <130 mg/dL in patients with definite CHD or two other CHD risk factors (Table 4).

The LDL-cholesterol level that is necessary to promote substantial or maximal atherosclerotic regression has not been established, but some investigators believe that an LDL-cholesterol level as low as 100 mg/dL may be considered an ideal goal. Thus, it may be desirable to strive for an LDL-cholesterol level considerably below the minimal target goals of 160 mg/dL or 130 mg/dL, particularly in patients with definite CHD or with other major risk factors, once the decision to institute drug therapy has been made. There is no current evidence or opinion to suggest that further lowering of LDL-cholesterol below 100 mg/dL will produce significant additional benefit.

Selection and Use of Drugs

Overview and General Approach.—The major drugs for consideration include the following: bile acid sequestrants (cholestyramine, colestipol); nicotinic acid; HMG CoA reductase inhibitors (lovastatin); gemfibrozil; and probucol.

A brief summary of the major characteristics of these drugs is provided in Tables 9 and 10.

The drugs of first choice for patients without concurrent hypertriglyceridemia (triglyceride, <250 mg/dL) are the bile acid sequestrants and nicotinic acid. These drugs have been found to reduce CHD risk and to be generally safe in long-term use. They are effective in lowering LDL-cholesterol. Nicotinic acid is preferred for patients with concurrent hypertriglyceridemia (triglyceride, ≥250 mg/dL), because it lowers LDL-cholesterol without exacerbating the hypertriglyceridemia. The bile acid sequestrants can also effectively lower LDL-cholesterol in these patients, but their administration as single drug therapy will sometimes cause substantial increases in serum triglycerides.

Lovastatin is the first available drug in a new class, the HMG CoA reductase inhibitors. It is very effective in lowering LDL-cholesterol levels, produces modest reductions in triglyceride levels, and is easy to administer. The clinical use of lovastatin has been under study for only a few years, and its long-term safety and effects on CHD end points have not yet been established. It is, therefore, not classed as a drug of first choice in this report, and some caution is appropriate in its use.

Gemfibrozil and probucol are other available drugs that are also not classified as drugs of first choice. These drugs are generally not as effective in lowering LDL-cholesterol as are the bile acid sequestrants, nicotinic acid, or the

Table 10.—Drugs Highly Effective in Lowering LDL-Cholesterol*

Drug	Starting Dose	Maximum Dose	Usual Time and Frequency	Side Effects	Monitoring
Cholestyramine, colestipol	4 g twice daily, 5 g twice daily	24 g/d, 30 g/d	Twice daily, within an hour of major meals	Dose-dependent upper and lower gastrointestinal tract	Dosing schedules of coadministered drugs
Nicotinic acid	100-250 mg as single dose	3 g/d, rarely, doses up to 6 g are used	Three times a day with meals to minimize flushing	Flushing, upper gastrointestinal tract and hepatic	Uric acid, liver function, glucose
Lovastatin	20 mg once daily with evening meal	80 mg/d	Once (evening) or twice daily with meals	Gastrointestinal tract and hepatic, miscellaneous, including muscle pain	Liver function, creatine kinase, lens

*LDL indicates low density lipoprotein.

HMG CoA reductase inhibitors. Moreover, these drugs have not been shown to reduce CHD risk and their safety for long-term use has not been established at this time. However, the results of a large clinical trial, the Helsinki Heart Study, evaluating the effects of gemfibrozil on CHD risk are expected soon.[59] If a clinically beneficial effect is seen, the recommended use of gemfibrozil will probably be expanded.

The cost of drugs may also warrant consideration. Cost should be viewed in relation to a drug's effectiveness and safety in cholesterol lowering. The following are the approximate yearly wholesale costs of drugs, derived from data in the 1986 Redbook; retail costs will be somewhat higher. Cholestyramine (Questran) at a daily dose of 16 g or colestipol (Colestid) at a daily dose of 20 g in bulk containers is $500 to $550; "generic" nicotinic acid at a daily dose of 3 g is $50, while Nico-Bid is $700; gemfibrozil (Lopid) at a daily dose of 1.2 g or probucol (Lorelco) at a daily dose of 1 g is approximately $375. Lovastatin is being marketed to the pharmacist at $1.25 per 20-mg tablet; at a dose of 40 mg/d, the yearly wholesale cost will be approximately $910.

Many patients with marked elevations of LDL-cholesterol will not be adequately controlled with single-drug therapy, and the use of combinations of drugs with synergistic mechanisms of action may be particularly effective in these patients. The mechanisms of action, clinical efficacy, and side effects of the drugs of first choice and the HMG CoA reductase inhibitors for the treatment of high-risk LDL-cholesterol levels are discussed in the following section. There then follows a more abbreviated discussion of the other drugs and of combination drug therapy.

Drugs of First Choice.—*Bile Acid Sequestrants: Cholestyramine and Colestipol.*—The major effect of the bile acid sequestrants is a lowering of the level of LDL-cholesterol. The sequestrants have the advantage that their use has been shown to reduce CHD risk in large-scale intervention trials and that long-term safety information is also available.[10,13] The sequestrants are not absorbed from the gastrointestinal tract and lack systemic toxicity. Thus, they are particularly suitable for treating younger patients, especially children and women considering pregnancy. The disadvantages of the sequestrants are related to the method of administration and the frequency of gastrointestinal side effects.

The primary action of the sequestrants, which are anion exchange resins, is to bind bile acids in the intestinal lumen; this interrupts the enterohepatic circulation of bile acids and leads to an increased hepatic synthesis of bile acids from cholesterol. Depletion of the hepatic pool of cholesterol results in an increase in LDL receptor activity in the liver. This in turn stimulates removal of LDL from plasma and lowers the concentration of LDL-cholesterol. Bile acid sequestrant therapy may increase hepatic VLDL production and thus increase the plasma concentration of triglycerides.

Cholestyramine and colestipol are both powders that must be mixed with water or fruit juice; they are taken in two (or, occasionally, three) divided doses with meals. The cholesterol-lowering effects of 4 g of cholestyramine are equivalent to those obtained with 5 g of colestipol. Decreases in LDL-cholesterol of 10% to 15% may be achieved with the initial suggested starting dosage schedule of 5 g of colestipol (or 4 g of cholestyramine) taken twice daily. In patients who do not respond adequately, the dose is increased gradually. Generally, the benefits of daily doses exceeding the equivalent of 16 g of cholestyramine are offset by poorer patient adherence and a greater incidence of gastrointestinal side effects. The response to therapy in individual patients is quite variable, but 15% to 30% reductions in the concentrations of LDL-cholesterol may be achieved with 16 to 24 g/d of cholestyramine or an equivalent dose of colestipol. The choice of one or the other of these drugs is dependent on individual patient preference based on taste and palatability. Cholestyramine is available in 9-g packets (each containing 4 g of cholestyramine and 5 g of orange-flavored filler) and in 378-g cans. Colestipol is available in 5-g packets and bottles containing 500 g, and there are no additives. The cost-per-unit dosage for cholestyramine is currently considerably less when it is purchased in bulk containers.

The bile acid sequestrants are contraindicated as single-drug therapy in patients with marked hypertriglyceridemia (triglyceride, >500 mg/dL) or patients with a history of severe constipation. The most common side effects associated with sequestrant therapy are gastrointestinal, and include constipation, bloating, epigastric fullness, nausea, and flatulence. Some suggestions for dealing with these side effects are provided in Appendix IV. These drugs are not absorbed, but they may interfere with the absorption of other anionic drugs if these are taken concurrently. It is generally advisable to take other medications at least one hour before or four hours after the bile acid sequestrants. The sequestrants can interfere with the absorption of digitoxin, warfarin, thyroxine, thiazide diuretics, beta blockers, and, potentially, many other drugs. Decreased absorption of fat-soluble vitamins and folic acid has been reported with prolonged high doses of the resins, primarily in patients with severe liver or small-bowel disease. Routine vitamin supplementation is not needed or recom-

mended in adult patients. Biochemical side effects include a modest increase in plasma triglyceride concentrations in many patients and an occasional mild and usually transient increase in alkaline phosphatase and transaminase.

Nicotinic Acid.—The water-soluble B vitamin, nicotinic acid, has been used to lower plasma lipid levels for many years. Administration of nicotinic acid in the Coronary Drug Project was associated with a reduction in recurrent myocardial infarctions and in long-term total mortality.[11,53] Nicotinic acid lowers total and LDL-cholesterol and triglyceride levels and raises HDL-cholesterol levels. Decreases in total cholesterol levels of 25% may be observed. Nicotinic acid decreases the hepatic production of VLDL and, ultimately, the production of LDL-cholesterol. Nicotinamide is not effective in lowering LDL-cholesterol and cannot substitute for nicotinic acid.

Nicotinic acid is a very effective drug that requires considerable physician and patient education (Appendix IV). Although it has frequent side effects, these are generally reversible on reducing the dose or discontinuing the drug. Because of its proven efficacy and safety, the efforts required to use this agent are justified.

Nicotinic acid is the least costly of all the currently available agents. Side effects, especially flushing of the skin, often limit acceptance by patients. The flushing is prostaglandin mediated and can be significantly decreased by pretreatment with aspirin or nonsteroidal anti-inflammatory drugs. Tolerance to this flushing develops rapidly over several weeks. Flushing is greatly reduced by slowly increasing the dose of nicotinic acid and avoiding administration on an empty stomach. The use of sustained-release preparations will also reduce flushing, but the cost is considerably greater.[54] Flushing will return if doses are omitted from the prescribed schedule.

Nicotinic acid therapy is generally initiated with a single dose of 100 to 250 mg/d. This initial dose is usually given after dinner to minimize problems with flushing during normal daily activities. The frequency of dose and total daily dose is slowly increased every four to seven days until the first-level therapeutic dose of 1.5 to 2 g/d is reached. If the LDL-cholesterol is not lowered sufficiently, the dose should be increased to 3 g/d (1.0 g three times per day). In patients with marked elevations of plasma cholesterol, a higher daily dose up to 6 g/d is occasionally used.

Hyperuricemia and abnormalities in liver function studies are other common adverse effects, but are more likely with higher doses of nicotonic acid. Hyperglycemia and a number of gastrointestinal side effects occasionally occur. Liver function, blood glucose, and uric acid levels should be evaluated before beginning nicotinic acid and after reaching therapeutic dosage or increasing the dose level. The medication is supplied in 50-, 100-, and 500-mg tablets. The latter dosage is preferred for chronic therapy. Contraindications to nicotinic acid therapy include peptic ulcer, hepatic disease, and gouty arthritis or significant hyperuricemia.

New Drugs: Inhibitors of HMG CoA Reductase.—The discovery of specific competitive inhibitors of the rate-limiting enzyme in cholesterol biosynthesis (HMG CoA reductase) has opened up a new avenue of therapy for patients with primary hypercholesterolemia.[55,56] A number of drugs in this category are currently being evaluated including lovastatin, simvastatin, and pravastatin. Of these, lovastatin has been most extensively studied in humans and has recently been approved for marketing. Long-term safety information is limited or not available, and thus caution in its use is recommended. This is especially true for individuals who are not at high risk.

Although the effects of HMG CoA reductase inhibitors on CHD incidence have not yet been established, mean reductions in LDL-cholesterol of 25% to 45% have been noted in both familial and nonfamilial forms of hypercholesterolemia. The HMG CoA reductase inhibitors increase LDL receptor activity in the liver and increase the rate of receptor-mediated removal of LDL from plasma. Additionally, the production of LDL is also decreased. Patients are generally started on 20 mg of lovastatin once daily with the evening meal. The dose may be increased to 40 and then to 80 mg/d as a single evening dose or divided (twice a day) doses with meals. The cholesterol-lowering effects of lovastatin have persisted for the duration of the observed treatment periods up to two to four years.

Lovastatin at doses of 20 to 80 mg daily has been well tolerated. Reported side effects (often transient) to date have included changes in bowel function, headaches, nausea, fatigue, insomnia, skin rashes, and myositis (myalgia associated with markedly elevated creatine kinase [CPK] levels), which collectively have occurred in less than 5% of treated patients. Biochemical changes have included increases in transaminase and CPK levels. Approximately 1.9% of patients have developed persistent increases in transaminase levels of greater than three times normal after three to 16 months of therapy, requiring discontinuance of therapy. Careful monitoring of liver function studies is essential. Lovastatin does not impair steroid hormone production. There is a concern about the possibility that there may be effects on formation of lens opacities; although no effects have been detected to date in humans, this is still being investigated. Baseline and regular follow-up evaluation of the lens should be done.

If long-term safety can be satisfactorily established, these inhibitors of cholesterol biosynthesis will represent a major advance in the therapy of hypercholesterolemia. These agents are extremely effective in reducing LDL-cholesterol concentrations and, from the patient's point of view, are easy to take.

Other Drugs.—*Gemfibrozil.*—Gemfibrozil, a fibric acid derivative, is approved by the Food and Drug Administration primarily for triglyceride lowering to reduce the risk of pancreatitis, and not for routine use in lowering cholesterol to reduce the risk of CHD. It is sometimes used as single drug therapy in patients who do not tolerate the resins or nicotinic acid, and is occasionally used in combination with first-choice drugs (see the section on "Combined Drug Treatment"). The long-term safety and effects of gemfibrozil on CHD risk are still being evaluated in clinical trials. Preliminary evidence for long-term safety of gemfibrozil is available in the interim report of the Helsinki Heart Study.[59] This is a large, placebo-controlled study to evaluate the effect of this drug on CHD risk, and the results should be announced in the near future. If a clinically beneficial effect is demonstrated in this clinical trial, the recommended use of gemfibrozil will probably be expanded.

Gemfibrozil is primarily and highly effective in lowering triglycerides, and there is an associated increase in HDL-cholesterol. Because of the effect of this drug on HDL-cholesterol, the results of the Helsinki Heart Study may be of particular interest. To date, increases of HDL-cholesterol induced by treatment have not been conclusively shown to be associated with a decreased risk of CHD. A decrease in LDL-cholesterol of 10% to 15% may be seen in patients without elevated triglycerides treated with gemfibrozil. An increase in LDL-cholesterol may be seen in primary hypertriglyceridemia, and either increases or decreases in LDL-cholesterol may be seen in patients

with elevated levels of both cholesterol and triglycerides. Gemfibrozil is well tolerated in most patients. The more common side effects include a variety of gastrointestinal symptoms, and occasional changes in hematologic parameters and liver function tests are noted. Gemfibrozil does potentiate the effects of oral anticoagulants and increases biliary lithogenicity. It is available as 300-mg capsules, and the usual dosage is 600 mg twice daily.*

Probucol.—Probucol therapy usually reduces LDL-cholesterol by about 8% to 15%, but there is also an associated reduction in HDL-cholesterol of up to 25%. There are no extensive, long-term clinical studies currently available for assessing probucol's safety or effect on CHD risk. Preliminary information indicates that probucol may inhibit the oxidation and tissue deposition of LDL. Probucol increases the rate of LDL catabolism, part of which may involve nonreceptor-mediated pathways.[57] The role of probucol in the treatment of patients with high LDL-cholesterol is uncertain because of concerns about the reduction in HDL-cholesterol, but xanthoma regression has also been reported as the HDL-cholesterol level decreases. Probucol is sometimes used as single drug therapy in patients who do not tolerate other drugs, and is occasionally used in combination with first-choice drugs (see the section on "Combined Drug Treatment").

Probucol is generally well tolerated, and side effects (including diarrhea, flatulence, abdominal pain, and nausea) occur in less than 5% of patients. Probucol causes prolongation of the QT interval, and the drug should be regarded as contraindicated in patients with electrocardiographic findings suggestive of ventricular irritability, with an initially prolonged QT interval, or taking other drugs that prolong the QT interval. Probucol is stored in adipose tissue, and blood levels fall slowly after therapy is discontinued. It is available in 250-mg tablets, and the usual dose is 500 mg twice daily.

Clofibrate.—Clofibrate, like gemfibrozil, is a fibric acid derivative. It is approved by the Food and Drug Administration primarily for triglyceride lowering to reduce the risk of pancreatitis, and not for routine use in lowering cholesterol to reduce the risk of CHD. Its effects on lipids and lipoproteins and its side effects are generally similar to those described above for gemfibrozil. Clofibrate is used less frequently than gemfibrozil, however, because of reports of long-term toxicity in clinical trials, particularly the World Health Organization Clofibrate Study.[58]

*Additional Note: The following statement was prepared by the Steering Committee of the Cholesterol Adult Treatment Panel (Drs Goodman, Cleeman, Brown, Grundy, Hulley, Hunninghake, and Rifkind) six weeks following the final approval of the report by the National Cholesterol Education Program Coordinating Committee:

Subsequent to the formal endorsement of this report by the National Cholesterol Education Program Coordinating Committee, the results of the Helsinki Heart Study were reported (Frick, MH, et al, *N Engl J Med* 1987;317:1237-1245). This randomized, double-blind five-year trial tested the clinical efficacy and safety of gemfibrozil, 600 mg twice daily, vs placebo in 4081 asymptomatic middle-aged men with elevated blood cholesterol levels. Gemfibrozil moderately reduced the serum levels of total and LDL-cholesterol, and also reduced triglycerides and increased HDL-cholesterol levels. The incidence of CHD was reduced by 34% in the drug-treated group ($P<.02$). This trial thus demonstrates the clinical efficacy and safety of gemfibrozil in reducing coronary risk in patients with high cholesterol levels. In view of these results, it would be reasonable for physicians to consider the use of gemfibrozil more readily when selecting drugs for patients with high cholesterol levels who meet the criteria for drug treatment. Gemfibrozil may be particularly useful, as an alternative to nicotinic acid, in patients with high-risk LDL-cholesterol levels who also have borderline hypertriglyceridemia (triglyceride levels, 250 to 500 mg/dL) and low HDL-cholesterol levels. More extensive review and evaluation of the results of the Helsinki Heart Study may further clarify the place of gemfibrozil in the treatment of patients with high blood cholesterol.

Miscellaneous Drugs.—These drugs are not recommended for general use.

Neomycin.—Neomycin is a nonabsorbable aminoglycoside antibiotic with cholesterol-lowering effects. Reductions in LDL-cholesterol levels of 20% to 25% have been reported. Side effects include diarrhea and abdominal cramps. Neomycin also has a potential to cause serious ototoxicity and nephrotoxicity. This drug is not approved by the Food and Drug Administration as a lipid-lowering agent, and its use should be considered investigational.

Dextrothyroxine.—Dextrothyroxine, the optical isomer of L-thyroxine, moderately lowers the concentrations of LDL-cholesterol, but does so at the expense of making the patient moderately hyperthyroid. Dextrothyroxine is approved by the Food and Drug Administration for use in selected young adults with primary hypercholesterolemia who are unable to take other effective lipid-lowering drugs. It is not recommended for use in this report because of the high incidence of adverse cardiovascular effects and hypermetabolic effects. Other available drugs have a more favorable benefit/risk ratio.

Investigational Drugs.—There is currently a flurry of activity in the development of new cholesterol-lowering agents. There are several new HMG CoA reductase inhibitors in various stages of development. Simvastatin and pravastatin are currently being extensively investigated in clinical trials. A number of newer fibric acid derivatives are available in Europe, and bezafibrate and fenofibrate have been fairly extensively evaluated in the United States. They appear to be more effective in lowering LDL-cholesterol than gemfibrozil or clofibrate.

Combined Drug Treatment.—If the response to single-drug therapy with one of the drugs of first choice is inadequate, combined drug therapy using two agents, preferably with synergistic mechanisms of action, should be considered to further lower LDL-cholesterol.[12,56,60] Experience with such drug combinations is somewhat limited, and it might be advisable to undertake such combination therapy in consultation with a lipid specialist. In patients without concurrent hypertriglyceridemia, the combination of a bile acid sequestrant with either nicotinic acid or lovastatin has the potential of lowering LDL-cholesterol by 45% to 60%. The addition of probucol or gemfibrozil to bile acid sequestrant therapy may occasionally be beneficial, but the efficacy of these combinations is significantly less than the abovementioned combinations. The combination of sequestrants and probucol may result in fewer gastrointestinal complaints.

For patients with both increased LDL-cholesterol levels and hypertriglyceridemia, nicotinic acid and lovastatin represent initial drugs of choice. Lovastatin and nicotinic acid can also be used in combination, or either of these two drugs can be combined with a bile acid sequestrant to obtain a possible additional 20% to 25% reduction in LDL-cholesterol. As yet, there is very little experience with the combination of lovastatin and nicotinic acid in terms of possible adverse effects such as hepatotoxicity. The addition of gemfibrozil to a bile acid sequestrant, lovastatin, or nicotinic acid will usually produce additional lowering of triglycerides, but the effect on change in LDL-cholesterol levels is quite variable. More experience is required with the combination of lovastatin and gemfibrozil to see if there is an increased risk of myositis.

Other Approaches.—Effective control of elevated levels of LDL-cholesterol will be attainable in the majority of patients using the primary drugs and drug combinations discussed above. Patients who do not achieve adequate cholesterol reduction after this type of therapy should be

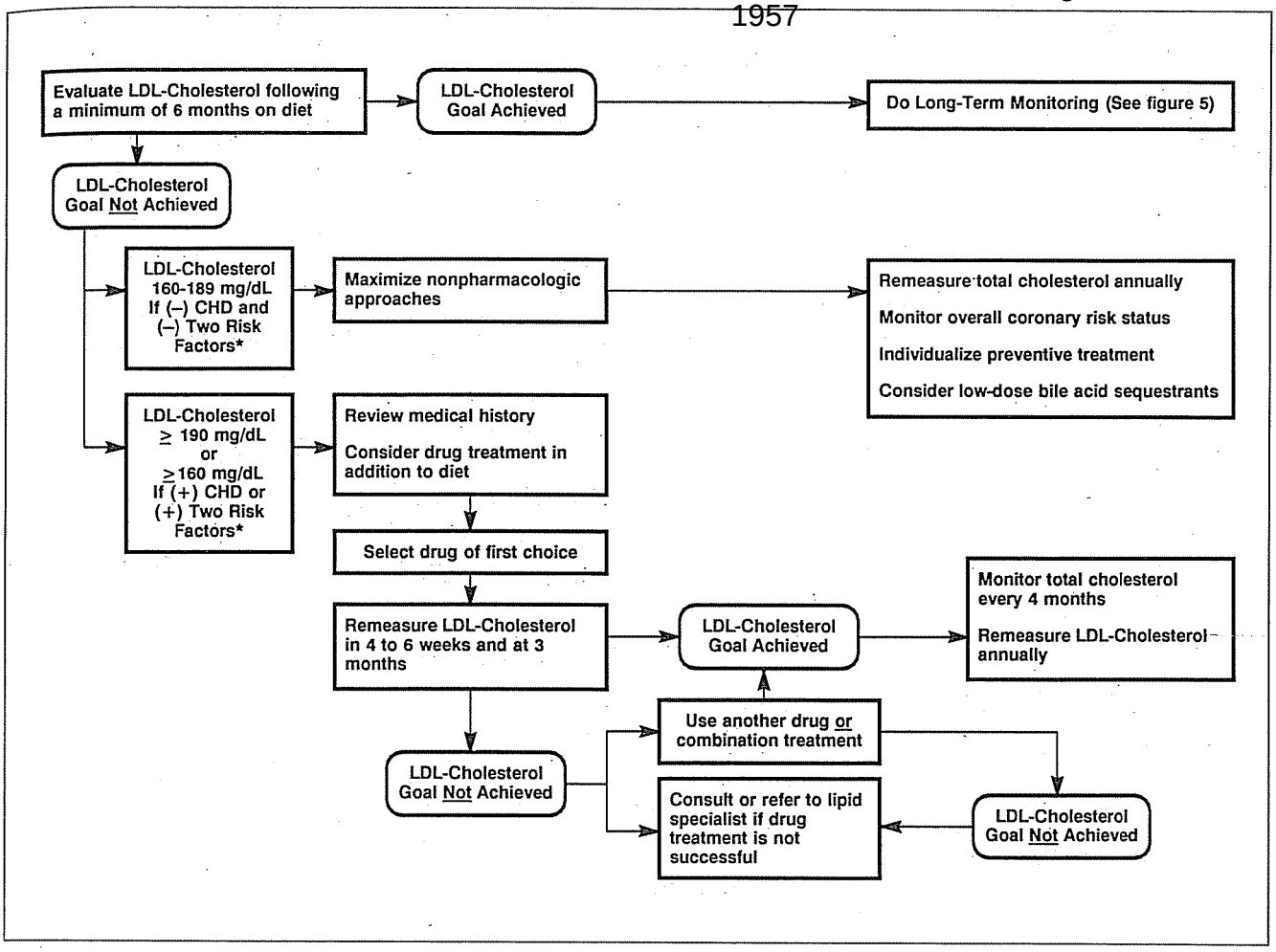

Fig 6.—Drug treatment. Asterisk indicates one of which can be male sex (Table 4); LDL, low density lipoprotein; CHD, coronary heart disease.

referred to a specialist in lipid disorders. In addition to investigational drugs or other drug combinations, other approaches may be indicated. In patients with FH, plasmapheresis (either simple plasma exchange or plasma exchange with some type of affinity chromatography) has been used to selectively remove LDL from plasma. A surgical procedure, partial ileal bypass, has occasionally been used to lower LDL-cholesterol in heterozygous FH. In homozygous FH, portacaval shunt and liver transplant have been employed.

Monitoring and Followup of Patients

Drug therapy is usually not begun until patients have had at least a six-month trial of dietary therapy. The decision to begin drug therapy should be reviewed with the patient along with the respective benefits and side effects of the appropriate drugs.

It is important to have a minimum of two determinations of lipoprotein levels during the last one to two months of maximum dietary therapy, because the efficacy of drug therapy needs to be judged against an accurately determined baseline. With good drug adherence, maximum lowering of LDL-cholesterol is obtained within four weeks of initating drug therapy. Thus, the first follow-up LDL-cholesterol determination should be made four to six weeks after initiating drug therapy. A second measurement should be done at three months; a minimum of two lipoprotein determinations is essential for evaluating drug efficacy. The mean of these two determinations and a careful assessment of drug adherence should be used to initially judge the effectiveness of drug treatment. After the response to drug therapy has been established and if the response is adequate, then the patient should be seen for a follow-up visit approximately every four months, in order to monitor for side effects and assess the patient's status and response to therapy. A lipoprotein profile (LDL-cholesterol measurement) at yearly intervals will usually be adequate; measurement of serum total cholesterol will usually suffice for the interim visits (Fig 6). In the course of long-term monitoring, if the total cholesterol or lipoprotein determination at a particular visit is out of keeping with the patient's previous values, the determination should be repeated to confirm the level.

The previously obtained laboratory work and medical history and physical examination should be reviewed before initiating drug therapy to see if any tests should be repeated or whether additional tests are required. The laboratory indications of adverse drug effects are generally manifested by changes in blood count, or liver or kidney function studies. These tests should definitely be repeated within one to three months of initiation of drug therapy, depending on the drug used, and at four- to 12-month

intervals thereafter. Additional testing may be required if abnormalities are noted, or if a high dose of drug is being used, or because of the known toxicity profile of a given drug (see previous discussion of major adverse effects for individual drugs). For example, more frequent transaminases are indicated when using lovastatin and more frequent uric acid and liver function determinations with higher doses of nicotinic acid.

The use of the bile acid sequestrants and nicotinic acid requires frequent observation or contact with the patient during the early stage of treatment. Clinic visits and/or telephone contact is usually indicated at least at monthly intervals for three to four months. Lovastatin requires continuing liver function and lens evaluation. Thus, there is a need for judgment regarding the frequency of visits and observation during the early phases of drug therapy. When the final drug regimen has been established, follow-up visits should continue at four-month intervals to promote adherence. Many of the routine patient contacts may not need direct physician involvement but may be handled instead by physician's assistants, nurses, pharmacists, or dietitians.

If the patient has had at least a 15% decrease in LDL-cholesterol and is tolerating the drug but has not achieved the minimal target goal for LDL-cholesterol, consideration should be given to adding another drug as discussed in the "Combined Drug Treatment" section. If the patient has not had a 15% decrease in LDL-cholesterol or is not tolerating the drug, the physician should either switch to another drug or proceed to combination therapy, if necessary. Consultation with a lipid specialist may be useful in the management of patients with persistently high LDL-cholesterol levels despite dietary and drug therapy.

Adherence to Drug Therapy

General Comments.—Drug therapy is likely to continue for a lifetime or for a very prolonged period of time. Hence, the patient must be well informed about the goals of drug treatment and the side effects of medication. The need for a long-term commitment must be emphasized. When dealing with the selection of bile acid sequestrants vs newer, "easier" drugs, safety must be emphasized. It is important to start with small doses of the drugs, especially when using sequestrants and nicotinic acid. The patient must have time to adapt to the drug regimen, and any difficulties must be remedied before proceeding to higher doses. Health professionals who are already involved in patient education would be a logical source of help for the patient who is having problems with side effects. The initial experience with a regimen is likely to predict long-term adherence.

The frequency of medication intake and its impact on life-style must be frankly discussed. The planned regimen should attempt to minimize changes in daily life-style. Reinforcement of adherence by periodic laboratory monitoring and reassurance is essential. There is also a need for patience, an adequate amount of time, and understanding on the part of the health professional. It must be emphasized to patients that the ultimate responsibility for management is theirs, and communication with the appropriate health professional is essential when problems arise. The importance of diet in addition to drugs must continue to be emphasized. Some practical suggestions concerning adherence are summarized in Appendix IV.

Patient Counseling/Assessment of Adherence.—The management of a risk factor like elevated serum cholesterol is multifactorial and in the ideal treatment setting would call on the expertise of a variety of professionals. Time and resources dictate a more prudent approach. Drug therapy for many patients can be successfully managed by the physician in his or her office along with the assistance of an office health professional who has skill and experience in teaching patients and some understanding of the side effects of drugs and approaches to their management. This person will generally be a nurse, or a nursing or physician's assistant. The community pharmacist is also a valuable resource for patient education. Additional educational efforts are usually required to ensure the successful utilization of the bile acid sequestrants and nicotinic acid, as compared with the other cholesterol-lowering drugs. There should be regular communication with the supervising physician, but many other health professionals can effectively educate the patient. A sensitive, caring individual who routinely sees the patient (constant caretaker model) and develops the patient's trust is often an important component of an effective adherence counseling program.

It is important that community health care providers utilize appropriate specialist consultation. Lipid specialists are available in most large metropolitan areas. Of major importance is the maintenance of continuing education in the cholesterol area, where knowledge is rapidly growing. Furthermore, consultation on an ongoing basis may be sought so that more difficult cases or situations can be reviewed and consultation obtained for planning treatment. If the target treatment goals for LDL-cholesterol are not achieved or if the patient is having considerable problems with side effects of medication, referral to a specialist in lipid disorders may be indicated. This is especially important if the patient has definite CHD, a genetic disorder with severe hypercholesterolemia, or other major risk factors. It is difficult to provide the best care possible through the use of a multidisciplinary team and also control the cost of treatment to the patient. Minimizing the number of office visits, limiting the number of direct care providers, and using the least costly provider with the broadest skills for routine care will help. Maximizing the response to dietary therapy will minimize the need for costly drug therapy. The use of standardized teaching materials that can be adapted to individual needs, and inexpensive follow-up between office visits (eg, telephone or postcard exchanges) may help patients successfully follow a regimen that has been tailored to their circumstances and that has every likelihood of effectively lowering their elevated cholesterol levels.

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APPENDIXES

Appendix I

Table I-1.—Corresponding Levels of Lipids

Cholesterol		Triglyceride	
mg/dL	mmol/L	mg/dL	mmol/L
35	0.9	250	2.8
130	3.4	400	4.5
160	4.1	500	5.6
190	4.9	1000	11.3
200	5.2	...	...
240	6.2	...	...